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Defence Warriors: Exploring the crosstalk between polyamines and oxidative stress during microbial pathogenesis

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ABSTRACT

Microbial infections have been a widely studied area of disease research since historical times, yet they are a cause of severe illness and deaths worldwide. Furthermore, infections by pathogens are not just restricted to humans; instead, a diverse range of hosts, including plants, livestock, marine organisms and fish, cause significant economic losses and pose threats to humans through their transmission in the food chain. It is now believed that both the pathogen and the host contribute to the outcomes of a disease pathology. Researchers have unravelled numerous aspects of host-pathogen interactions, offering valuable insights into the physiological, cellular and molecular processes and factors that contribute to the development of infectious diseases. Polyamines are key factors regulating cellular processes and human ageing and health. However, they are often overlooked in the context of host-pathogen interactions despite playing a dynamic role as a defence molecule from the perspective of the host as well as the pathogen. They form a complex network interacting with several molecules within the cell, with reactive oxygen species being a key component. This review presents a thorough overview of the current knowledge of polyamines and their intricate interactions with reactive oxygen species in the infection of multiple pathogens in diverse hosts. Interestingly, the review covers the interplay of the commensals and pathogen infection involving polyamines and reactive oxygen species, highlighting an unexplored area within this field. From a future perspective, the dynamic interplay of polyamines and oxidative stress in microbial pathogenesis is a fascinating area that widens the scope of developing therapeutic strategies to combat deadly infections.

1. Introduction

Microbes are ubiquitous entities of nature, occupying diverse ecological niches and sharing countless interactions amongst each other and with higher eukaryotes as symbionts, predators, and competitors. Apart from nature, they reside in multiple hosts as the so-called "commensals" regulating several host cellular and physiological functions. Animals and other higher eukaryotes are rich sources of nutrients for these microscopic creatures, providing sugars, amino acids, nitrogen-rich compounds such as ammonia, etc [1]. Apart from the commensals, certain microbes are capable of causing disease in their hosts. With the origin of the "germ theory", only microbes that meet the set Koch's postulates were classified as pathogens. Over the years with advancements in host-microbe interactions, theories to classify microbes as pathogens have also reformed. As defined by the "damage response framework" of microbial pathogenesis, the pathogenesis arises due to host and microbe interaction, and host damage is an outcome of the pathogenesis, while the damage can be due to both the microbial and host factors [2]. However, microbial pathogenicity is variable depending on the extent of damage caused by the interactions between a host and a particular pathogen. Thereby describing infection as the ability of the pathogen to persist and multiply within the host while eventually leading to damage [3]. Thus, it can be considered that the evolution of the pathogenesis of microbes is due to the foraging of nutrients from rich animal sources while eventually sparkling disease pathologies [1].

Microbial pathogens are a cause of illness and morbidity worldwide. The WHO has issued a priority list of pathogens associated with severe illness and fatalities. The updated bacterial and pathogen priority list issued in 2024 is an important tool to educate and fight the global rise of antimicrobial resistance. It includes the names of *Mycobacterium*

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tuberculosis, Salmonella, Shigella, Pseudomonas, Staphylococcus aureus and *Neisseria gonorrhoeae* [4]. On the other hand, the WHO fungal pathogen priority list released in 2022 was due to the substantial rise in fatal fungal infections during the COVID-19 pandemic and the subsequent increase in resistance to anti-fungal drugs [5]. Over 1.5 million deaths are caused worldwide by the disease caused by fungal pathogens [6]. Another major cause of mortality in the healthcare sector is healthcare-associated infections, also called nosocomial infections, leading to around 40,000 deaths per year. The incidences are increasing at 25 % in developing countries and 5–15 % in developed countries [7]. The antimicrobial-resistant strains of ESKAPE (*Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinatobacter baumannii, Pseudomonas aeruginosa, Enterobacter aerogenes*) pathogens are the major causes of nosocomial infections and associated deaths worldwide. Further, a recent cohort study accounted for the highest incidence of respiratory viral diseases caused by rhinoviruses and common cold Coronaviruses both before and post-COVID-19 pandemic [8]. The pathogenesis of these critical pathogens involves stealthy strategies to evade the host immune system, the ability to invade the host, competing with the resident microbiota to colonise the niche, and modulating host metabolic pathways to ensure nutrient availability and persistence. Multiple players are critical for the successful pathogenesis and infection by the pathogen, such as the elimination of motility structures as in *Salmonella* that sheds flagella when inside its host cells to prevent TLR-mediated immune responses, mutations of the surface protein structures as in SARS-Cov2, yeast to hyphae transition in *Candida* [8–10] and translocation of effector proteins to modulate host cellular processes [11]. One critical molecular player in host-pathogen interactions is the family of polyamines. Polyamines are polycationic small amines ubiquitous in nature and are key molecules regulating numerous cellular processes in both prokaryotes and eukaryotes. Studies over the years have linked these polycationic molecules to several aspects of host-pathogen interactions, particularly their involvement in microbial pathogenesis. Moreover, various host factors, such as oxidative stress, nitrosative stress, complement systems, pH changes, autophagy, humoral immune strategies, etc., employed to limit the infection are critical in such interactions. Pathogens occupying the host niches and counteracting the host immune strategies evolve to develop resistance and subsequently conquer the host in the arms race.

The significant rise in severe pathogen infections and associated mortality worldwide urges the need to delve deep into the unknown facets of host-pathogen interactions and widen the horizon. Understanding the pathogenesis, identifying novel drug targets and developing sustainable treatment strategies to curb such devastating infectious diseases is paramount. In this review, we integrate the recent advances in a comprehensive review of the polyamines in microbial pathogenesis from diverse pathogen and host perspectives. Polyamines are known to function by interacting with several biomolecules and molecular players. This review primarily centres on the unique interplay of polyamines and oxidative stress in host-pathogen interactions. We further highlight the key functions of polyamines in interactions of the commensals and pathobionts within the host niches, underscoring the host-commensal-pathogen interaction paradigm. We conclude by consolidating the present therapeutic interventions targeting polyamines and oxidative stress pathways in curing multiple infections and explore this arena as a source of anti-pathogen drug discoveries and identification of novel and sustainable strategies to curb deadly pathogen infections.

2. Polyamines in infectious diseases

With the discovery of polyamines by Antonie Van Leeuwenhoek in 1678, a new arena of research has emerged in cell biology to delve into the functions of these polycationic molecules (Fig. 1). These molecules are ubiquitously present in all living forms, and their significant levels within the eukaryotic and prokaryotic cells have led to a substantial number of research to delineate the role of these critical molecules in a wide array of lifeforms [12,13]. The levels of polyamines within the cells change with the different conditions and are associated with a wide range of functions [14]. The function of polyamines has been deeply studied in mammals. However, with recent advancements in this field, the critical role of polyamines has also been explored in other organisms

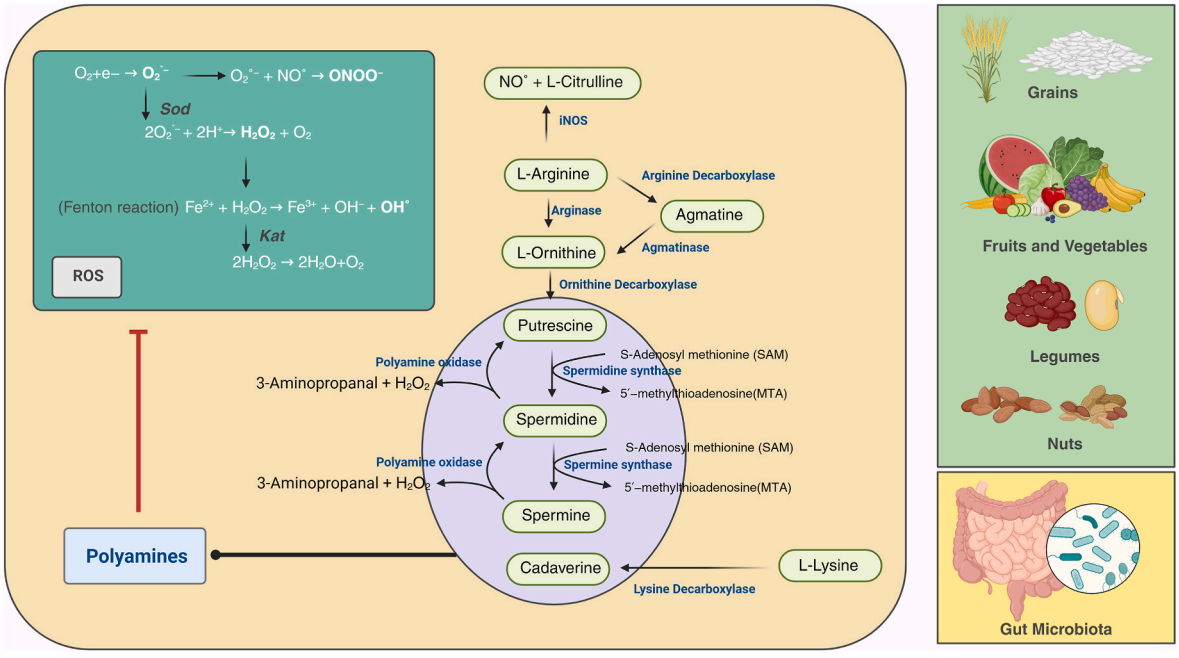

Fig. 1. The molecular reactions and metabolism of polyamines and ROS in cells- Polyamines and ROS are synthesized by distinct molecular reactions. The polyamines are synthesized from L-Arginine as the main precursor. They are also obtained from various dietary sources. Besides, the gut microbiota play a critical role in metabolising dietary components and produces polyamines for absorption, that is available to both the host as well as enteric pathogens. ROS members include the Hydrogen peroxides (H_2O_2) and superoxide anions ($O_2^{\cdot-}$), toxic hydroxyl radicals (°OH), Nitric oxide (NO°) and the peroxynitrites ($ONOO^-$).

such as plants, bacteria, viruses, fungi, protozoa and a few other invertebrates. In mammals, they are linked to angiogenesis, growth and development, endocrine, reproductive, digestive and many more physiological processes [15]. Polyamines also play a key role in cancer development and tumour progression in the mammalian system [16,17]. New investigations led to the exploration of their function in infectious disease pathogenesis. Microbes also have significant levels of polyamines, where these small polycationic molecules regulate their growth and virulence properties [18–21]. Bacterial pathogens such as *Salmonella* Typhimurium, *Streptococcus pneumoniae, Helicobacter pylori, Vibrio cholerae,* and many more utilize polyamines for their pathogenesis and infection into their corresponding hosts [19,22–24]. Recent studies highlight the role of polyamines in the expression and construction of the specialised Type 3 secretion system (T3SS) encoded by the *Salmonella* Pathogenicity Island-1(SPI-1) and also the surface adhesive structures, thereby aiding in adhesion and invasion into the intestinal epithelial cells [25,26]. Similarly, in the fish pathogen *Edwardsiella piscicida*, which infects humans through contaminated food and water, polyamines contribute to immune evasion by upregulating host cytosolic spermine levels. This accumulation inhibits K^+-ion efflux-dependent NLP3 inflammasome activation, allowing the pathogen to persist within the host [27]. Additionally, *Acinetobacter baumannii*, a critical nosocomial pathogen, encodes a novel polyamine transferase enzyme that plays a key role in motility and biofilm formation, further supporting its survival and virulence [28].

Most viral pathogens utilize host-derived polyamines to replicate, package, and stimulate viral proteins [29–32]. Inhibition of polyamine biosynthesis has been shown to significantly reduce the infectivity of several viruses, including Dengue virus (DENV), Hepatitis C virus (HCV), Japanese encephalitis virus (JEV), Herpes simplex virus (HSV), and Chikungunya virus (CHIKV). [33]. Additionally, HIV infection upregulates polyamine synthesis genes, contributing to T-cell dysfunction, while polyamine-mediated hypusination of eIF5α is essential for Ebolavirus gene expression and replication [34,35]. Notably, blocking polyamine production using DFMO results in impaired attachment and entry of Coronaviruses into host cells [36].

The protozoan parasites such as *Trypanosoma cruzi, Trypanosoma brucei, Trichoma vaginalis, Leishmania* spp. and *Plasmodium* spp., also depend on polyamine biosynthesis and transport for survival and virulence, making these pathways promising drug targets for treating insect-borne human diseases [37–40]. *n T. cruzi,* disruption of polyamine transporters leads to reduced infectivity and increased susceptibility to trypanocidal drugs. The anti-protozoal drug pentamidine effectively decreases parasite burden in mouse heart tissue and reduces *T. cruzi* viability and proliferation *in vitro* by inhibiting polyamine transporters. [41,42]. Similarly, *Leishmania donovani* strains lacking ornithine decarboxylase, a key enzyme in polyamine biosynthesis, show impaired infectivity in macrophages and reduced parasitemia in the liver and spleen of infected mice [43]. These findings highlight the critical role of polyamines in pathogen survival and their potential as therapeutic targets.

In plants, polyamines are explored for the growth and cellular functions of the plant system, while they are extensively studied with respect to plant pathogen infections [12]. Polyamine oxidation serves as a key defense mechanism by generating reactive oxygen species (ROS) to combat invading microbes. However, the impact of polyamines on plant-pathogen interactions varies depending on the type of pathogen. [44,45]. For instance, in *Nicotiana tabacum*, infection by the necrotrophic fungal pathogen *Sclerotinia sclerotiorum* leads to elevated levels of putrescine and spermine in the leaf apoplast, which correlates with increased disease severity [46]. Conversely, infection with the biotrophic bacterium *Pseudomonas viridiflava* triggers an increase in apoplastic spermine levels, and its subsequent oxidation limits bacterial colonization, highlighting the differential outcomes of polyamine modulation in plant defense. [46]. Additionally, in tomato plants, the effector protein Brg11 from the phytopathogen *Ralstonia solanacearum* induces polyamine production in the leaf apoplast, activating a defense response against competing microbes but not against *R. solanacearum* itself. [47]. This underscores the complex and dynamic role of polyamines in shaping host-pathogen interactions across various plant species, making them a crucial element in the pathogenesis of infectious diseases.

3. Reactive oxygen and nitrogen species during infectious diseases

For a successful infection in the host, every pathogen must be able to persist and survive within the host tissues and cells. The host immune system employs multiple mechanisms to clear the invading pathogen; however, in several instances, the pathogen combats the host immune system and is able to persist within its host. The persistence is sometimes asymptomatic and recurs at a later stage, leading to chronic clinical symptoms [48,49]. In other cases, they result in acute infections and pathologies such as during *Pseudomonas, Klebsiella,* and *Influenza* infections [50,51]. Plenty of factors, including the host-derived and the pathogen's intrinsic attributes, contribute to the persistence and survival of the pathogen. One of the key innate immune strategies of the host is to generate oxidative and nitrosative stresses to kill the pathogen [52,53]. Host macrophages and neutrophils are the prime immune phagocytes that utilize the NADPH oxidases (NOX) to generate Reactive oxygen species (ROS) [54,55].

The existence of cyanobacteria and the occurrence of photosynthesis has led to the adaption of all life forms to the damaging by-product ROS of metabolic and respiratory pathways [56]. First introduced in the book 'Oxidative Stress' in the year 1985, and then in the review 'Biochemistry of Oxidative Stress', it indicates an imbalance in the ability of the cells to scavenge and detoxify the toxic ROS species [57–59]. These species include the Hydrogen peroxides (H_2O_2) and superoxide anions ($O_2^{\circ-}$), which are generated by univalent and divalent reductions of oxygen molecules [60]. While reaction of hydrogen peroxide with Ferrous ion by Fenton reaction results in toxic hydroxyl radicals ($^{\circ}OH$) [61]. The highly reactive superoxide anion is further enzymatically converted to lethal hypochlorous acid (HOCl) [54]. Like NOX, Nitric oxide synthase (NOS) catalyses the formation of Nitric oxide (NO°), the potent nitrosative stress molecule, which reacts with superoxide anion to generate peroxynitrites ($ONOO^-$) [62] (Fig. 1).

Infectious diseases are closely linked to redox biology, with ROS playing a critical role in host-pathogen interactions. ROS is primarily an innate immune stress molecule generated in response to an infection to kill and clear the pathogen. However, in certain instances, ROS acts as a boon for the pathogen, which they use to spread and disseminate within the host system. Bacterial pathogens such as *Salmonella, Klebsiella, Pseudomonas, Mycobacterium* and *Shigella* need to encounter oxidative stress within the host cells and are required to evade the host oxidative stress for pathogenesis [63,64]. Also, the common action of bactericidal antibiotics is to hydroxyl radicals through the Tri-carboxylic acid cycle, destabilisation of iron-sulphur clusters and Fenton reactions [65]. Several ROS switches are involved in the microbial pathogenesis that regulates the pathogen's ROS-sensing, adaptation and survival under these hostile conditions. Most pathogens are adept at sensing the environmental ROS through the established redox sensors, such as the SoxR/S and OxyR systems in bacteria. These sensors activate numerous genes such as the Type-3 secretion systems in *Vibrio parahaemolyticus,* antioxidants in *Salmonella, E. coli* and *Shigella,* and also toxins in *Streptococcus pneumoniae* (pneumolysins) [66–68]. In protozoan parasites, a major switch in adaption to oxidative stress is the increased synthesis of unique molecule trypanothiones, a conjugate of spermidine molecules with glutathione [69]. Trypanothiones acts as direct scavengers of ROS and most importantly, modifies cellular protein cysteine thiols and protects them from irreversible oxidation to sulfinic and sulfonic acids [70]. This phenomenon has recently been observed in bacteria as well, where glutathionyl-spermidine protects protein cysteine thiols [71].

Candida utilises a Glucose-enhanced oxidative stress resistance mechanism to counteract the ROS burst from the attacking host neutrophils during systemic infection [72].

Meanwhile, *Helicobacter pylori* infection induces oxidative stress and damage, facilitating its spread and gastric cancer progression [63,73]. *Chlamydia psittaci* infection in host macrophages leads to mitochondrial ROS generation and mitochondrial DNA damage. The damage triggers IFN-1 and IL-1β production through the cGAS-STING pathways, killing the pathogen and limiting the infection by the host immune system [74]. Likewise, a significant cause of mortality upon Influenza virus infection in neonates is the generation of ROS through IFN-1 production and pulmonary tissue damage [75]. Hepatitis C Virus infection (HCV) dysregulates the mitochondrial oxidative phosphorylation by blocking electron transfer from Complex-I, thereby increasing leaky reactive and nitrogen species generation [76]. However, the virus also evades oxidative stress by activating host glutathione peroxidases to prevent lipid peroxidation and enhance viral infectivity [77]. A study further shows that oxidative stress favours viral replication during the initial acute phase of infection, while in the chronic stage, it adversely affects by inducing autophagy [78]. The HCV protein NS3 triggers the host iNOS and NO° production and oxidative stress, which bring about mutations in most of the proto-oncogenes and tumour suppressor genes [79]. Together, these mutations contribute to the development of hepatocarcinoma [80]. Similar to HCV, the Dengue virus serotype 2 (DENV2) and Yellow fever virus infection also alter the redox balance within the host cells; it lowers the host antioxidant and increase the ROS [81,82]. Overall, oxidative stress is interrelated to infection and disease pathogenesis.

4. Polyamines and ROS/RNS interplay during pathogenesis

The notion of ROS/RNS in cellular physiology remains in the context of "oxidative stress and damage" however, scientists have shed light on an alternative role of these molecules. It is well established that ROS at high levels are harmful and toxic, but they are prime signalling molecules at low levels [83]. The "oxidative eustress" is the phenomenon where ROS is involved in redox sensing, signalling and regulation in the cells [84]. They are now known to be critical mediators of several signalling cascades such as the mitogen-activated protein kinase pathways (MAPK), phosphoinositide-2 kinase/protein kinase B (Akt) and the apoptosis signal regulating kinase-1 (ASK1) [85,86]. They also regulate numerous transcription factors such as activator protein 1 (AP-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), hypoxia-inducible factor 1α (HIF-1α) and nuclear factor erythroid-2 related factor 2 (Nrf2) [85]. While in plants as well, ROS activate the MAPK pathways and thereby transcription factors such as *ZAT* and *MYB* that further control the plant stress responsive genes to modulate lipid peroxidation, cell wall reinforcements etc. [87]. On the other hand, the small molecules polyamines are catabolized by Diamine oxidases (DAO), Polyamine oxidases (PAO) and Spermine/spermidine oxidases (SMOX) acting as ROS switches, that release hydrogen peroxide as a major product and the levels of hydrogen peroxide determines the overall response being beneficial or toxic to the cells [88]. As during abiotic and biotic stresses, polyamines are transported into the apoplast, where they are catabolized to generate hydrogen peroxide, while at low levels of hydrogen peroxide these act as signalling molecules to activate ROS dependent protective pathways to enhance tolerance in plants to abiotic stresses and killing of the pathogen in cases of infection [89,90]. The cross-talk between polyamines and ROS in plants further extends to control the transport across the plasma membrane by synergistically activating Ca^{2+}-ATPases, H^+ pumps and K^+ influx while suppressing a few non-selective cation channels, thereby mediating adaptive responses [91]. Apart from their direct interaction with each other, polyamines in most cases modulate the responses to ROS within the cells by regulating other molecular players, as the NADPH-oxidases. NADPH-oxidases are the prime enzyme complex that generates superoxide radicals and are upregulated by polyamines in *Arabidopsis thaliana* and *Prunus armeniaca* in response to microbial invasion [45,92]. Additionally, both NADPH-oxidases and polyamines synergistically generate ROS in the gut epithelial cells during *H. pylori* infection to limit the pathogen. But it is utilized by this pathogen as a blessing in disguise thereby inducing inflammation and carcinogenesis [93]. Interestingly, polyamines do show an unusual interplay with Endoplasmic Reticulum oxidative protein folding and ER stresses. Ero-1α is the key enzyme involved in the oxidative protein folding in the ER, which utilises hydrogen peroxides during the oxidation-reduction of Protein disulfide isomerases (PDI) [94]. From the perspective of defence, polyamines, on the other hand, act to quench, detoxify and neutralise the toxic ROS in cells as well as in microbial pathogens either by their direct action or by regulating antioxidants such as the superoxide dismutases and catalases [95–97]. In the following sections, we will further discuss the cross-talk of polyamines and ROS in microbial pathogenesis, pertaining to different pathogens and their corresponding diverse hosts and also summarised in Table 1.

4.1. Bacteria-host interactions

4.1.1. Human host

Bacterial pathogens thrive in a human host and encounter various environmental challenges. As a result, they have developed several adaptations to endure and proliferate under challenging circumstances. Bacterial physiology can alter significantly upon entry into its host and acquiring limited but necessary nutrients appears crucial for its cellular processes. Bacteria use multiple small molecule metabolites produced by themselves and from the host during colonization and infection, one being the polyamines. In bacteria, polyamine uptake, synthesis, and degradation processes are coordinated to regulate stringently intracellular polyamine levels [98]. Our understanding of polyamines and their role in the growth and virulence of human pathogens has recently increased substantially. Polyamines now appear to be more than trivial organic molecules whose functions are interchangeable or dispensable [99].

The most prevalent cellular polyamines, putrescine, spermidine, spermine, and cadaverine, are necessary for the regular growth and multiplication of bacterial cells [100]. Because of the polycationic nature of polyamines, they easily bind to anions in cells. Rather than binding to cytoplasmic proteins, intracellular polyamines are primarily observed as polyamine-RNA complexes and stabilize them. *Shigella flexneri* mutants of *tgt* cannot produce the modified nucleosides required for tRNA synthesis and are compromised in their virulence gene expression, which is restored by adding putrescine. It suggests that putrescine and virulence gene mRNAs interact directly, leading to more effective virulence gene translation and expression [101]. Also, the *speG* mutant of *Shigella,* which does not synthesize spermidine, showed attenuated survival in J774 macrophages, highlighting the role of spermidine in protection against oxidative stress [102]. When microbial pathogens encounter oxidative stress *in vivo*, they activate protective machinery as an adaptive response. One crucial enzyme that shields cellular nucleic acids from the harm caused by superoxide radicals is superoxide dismutase (SOD). Together with SOD, spermine and spermidine limit the damage that oxygen radicals cause to DNA strands by acting as free radical scavengers [103]. A recent study has shown that polyamine spermidine activates a stress response mechanism by regulating key antioxidant genes in *Salmonella*. Gene knockout strains for spermidine transport (*potA*, *potB*, *potC,* and *potD*) and synthesis (*speE* and *speD*) cannot mount an antioxidative response, leading to elevated intracellular ROS levels [104]. *Salmonella* Typhimurium uses spermidine to regulate the transcription of multiple transcription factors like *rpoS, emrR* and *soxR* involved in oxidative stress response [104]. Spermidine is conjugated with glutathione to form a specialised antioxidant in *Salmonella* that modifies proteins under oxidative stress and prevents protein oxidation and damage [104]. Similarly, in *E. coli,* spermidine

Table 1
The role of polyamines in microbial pathogenesis through their interaction with ROS and associated molecular mechanisms.

Bacterial Pathogens

Pathogen Name	Polyamines, associated players and targets	Effect of the Function	Consequence in Pathogenesis
Shigella flexneri (101,102)	tRNA synthesis; *speG* mutant affects bacterial spermidine levels	Restores virulence gene expression; offers oxidative stress protection	Enhances intracellular survival and virulence
Salmonella Typhimurium (26, 103, 104)	Antioxidant gene regulation via spermidine	Regulates *rpoS, emrR, soxR*; forms Glutathionyl-spermidine antioxidant	Manages ROS, modulates virulence gene expression
E. coli (105, 106)	*oxyR*, *katG*, *rpoN*, *hns*, *cra* via spermidine/putrescine	Enhances antioxidant response and gene translation	Increases survival under oxidative stress
Streptococcus pyogenes (108)	Uptake of host spermidine	Upregulates *mtsABC, sodM, npx* and virulence genes like *hasA*, *sagA*, *slo*	Promotes survival in macrophages
Streptococcus pneumoniae (109)	Spermidine uptake by *potABCD* transporter	Loss of spermidine uptake downregulates *treR*, causing redox imbalance	*in vivo* fitness
Pseudomonas aeruginosa (111)	Surface-localised spermidine	Protects membrane against H_2O_2 and polymyxin B	Confers resistance to oxidative and antibiotic stress
Mycobacterium tuberculosis (112, 113)	Arginine decarboxylase	Loss increases ROS and DNA damage	Decreases survival and enhances drug efficacy
Helicobacter pylori (96,114, 115, 116)	Host spermine oxidases (SMOX), *mir-124*	Chronic ROS generation by polyamine catabolism in host	Promotes DNA damage and gastric carcinogenesis
Enterotoxigenic B. fragilis (117,118)	Host polyamine metabolism (SMOX-mediated ROS)	Stimulates host DNA damage and chemokine synthesis	Drives colorectal cancer
Dickeya fangzhongdai (119)	*speA*, *speC* for polyamine synthesis	Loss decreases motility and plant cell wall degrading enzymes	Reduces virulence in taro and potato
Dickeya zeae (120)	*speA* gene and *potF* transporter for putrescine signalling	Affects motility, biofilm formation; exogenous putrescine rescues phenotype	Critical for invasion and rice seed infection
Pseudomonas syringae (121, 123)	Exogenous putrescine	Upregulates catalase, enhances H_2O_2 tolerance	Increases survival under oxidative stress
Pseudomonas viridiflava (124)	Host spermine oxidase	Increased apoplastic spermine; inhibition leads to higher colonization	Polyamine oxidation linked to biotrophic resistance
Pseudomonas cichorii (125)	Induction of polyamine metabolic genes and ROS	Hypersensitive response triggered	Contributes to localized defense in tobacco

Viral pathogens

Pathogen Name	Polyamines, associated players and targets	Effect of the Function	Consequence in Pathogenesis
Herpes Simplex Virus-1 (HSV-1) (133)	Nucleocapsid and envelope	Presence of spermine and spermidine in viral structure	Likely aids in viral stability and replication
Human Cytomegalovirus (HCMV) (134)	Host polyamine metabolism	Enhances polyamine metabolism for viral uptake	Supports viral replication and pathogenesis
Hepatitis C Virus (HCV) (135–137)	Host polyamine biosynthesis and catabolism	Induces ROS production by upregulating ROS-generating enzymes	Increased ROS leads to liver cirrhosis and carcinogenesis
Influenza A Virus (IAV) (138)	Host Polyamine biosynthesis and oxidative stress pathways	Inhibition of these pathways reduces viral survival	Polyamines are crucial for IAV survival
Porcine Epidemic Diarrhea Virus (PEDV) (139)	Host spermine oxidase and acetyl polyamine oxidase enzymes	Catalyses interconversions of spermidine and spermine, generating ROS	ROS aid viral infection and replication
HIV-1 (140,141)	Spermine oxidase and Amine oxidase system	Increases ROS production via HIV-1 Tat protein. Generates hydrogen peroxide from spermidine/spermine	Causes neuronal toxicity, linked to HIV-1-associated cognitive disorders Antiviral activity in semen and vaginal canal
Ebola Virus (EBOV), Chikungunya Virus (CHIKV), Zika Virus (ZIKV) (142)	eIF5α (translation elongation factor)	Uses spermidine-mediated hypusination for viral protein translation	Polyamines essential for viral protein synthesis
Coxsackievirus B3 (CVB3) (143, 144)	Viral capsid protein (V3) and proteases 2A, 3C	Adapts to polyamine depletion by mutation, aids in host protein cleavage	Stealth adaptation to host response and enhances viral infection
Cucumber Mosaic Virus (CMV) (153,154)	Spermine-responsive genes and ROS signaling	Triggers hydrogen peroxide signaling pathway	Enhances host defense response against CMV
Tobacco Mosaic Virus (TMV) (155,156)	Polyamines as a hydrogen peroxide source	Generates ROS in resistant tobacco cultivars	Provides symptomless resistance against TMV
Potato Virus X (157)	Polyamines and ROS signaling	ROS burst prevents severe symptoms	Symptomless resistance in Nicotiana tabacum
Maize Chlorotic Mottle Virus (MCMV) (149)	Polyamine oxidase (PAOX) gene regulation	miRNA-167 targets ARF30 to control PAOX expression	Restricts viral replication in maize
Citrus Tristeza Virus (158)	p33 viral protein-induced ROS generation	Restricts viral entry into the phloem	Limits viral spread in citrus plants
Sugarcane Mosaic Virus (SMV) (159)	Polyamine oxidases	Inhibition of enzyme promotes viral pathogenesis	Polyamine oxidase activation restricts SMV infection

Protozoan Pathogens

Pathogen Name	Polyamines, associated players and targets	Effect of the Function	Consequence in Pathogenesis
Trypanosoma cruzi, Trypanosoma brucei (162–168)	Trypanothione (spermidine + glutathione)	Antioxidant that quenches ROS	Promotes persistence in host and resistance to benznidazole, nifurtimox
Leishmania spp. (170, 178–180, 183)	Spermidine synthase, trypanothione pathway, exosome polyamines, *miR-372, miR-373* and *miR-520d*	Resists ROS; exosomes promote M2 macrophage phenotype	Promotes survival in host macrophages and chronic infection

(*continued on next page*)

Table 1 (*continued*)

Protozoan Pathogens			
Pathogen Name	Polyamines, associated players and targets	Effect of the Function	Consequence in Pathogenesis
Plasmodium falciparum (185)	Spermidine biosynthesis	Required for intra-erythrocytic stages; ROS tolerance via polyamine oxidase	Crucial for parasite survival; host uses ROS for counterattack
T. vaginalis (188)	Putrescine synthesis; spermine import	Alters redox-related proteome	Required for survival; inhibition leads to loss of redox balance and parasite death

Fungal pathogens			
Pathogen Name	Polyamines, associated players and targets	Effect of the Function	Consequence in Pathogenesis
Saccharomyces cerevisiae (199, 200)	*spe2* gene (spermidine/spermine synthesis)	Loss causes high ROS under aerobic conditions	Essential for growth and stress response
Penicillium marneffei (201)	SAM decarboxylase	Mutants show poor conidia formation and high ROS	Limits infectivity
Cryptococcus neoformans (204, 205)	Urease, spermidine synthase, arginine pathways	Mutants have lower melanin, higher ROS	Affects CNS infection and macrophage survival
Candida albicans (207, 208,210, 211)	*SPE1*, polyamine oxidase, *camCA1* caspase	Lowers polyamine synthesis and increases ROS production upon inhibitor treatments	Compromises survival in hosts and biofilms
Blumeria graminis (214)	Induces ODC, ADC in barley	Local polyamine and ROS production	Triggers a resistance response in plants upon a pathogen entry
Piriformospora indica (217)	Polyamine metabolism in plants	Enhances polyamine metabolism	Protects host plants from crown rot of wheat plants caused by *Fusarium pseuodograminearum*

and putrescine increased the expression of vital antioxidant genes, *oxyR* and *katG* genes, indicating the presence of 'polyamine modulon' in these bacteria [105]. Putrescine and spermidine are the key factors that control the translation and transcription of several gene targets by interacting with the negatively charged nucleic acids. They enhance the translation of several transcription factors, such as *rpoN* and *hns,* in *E. coli* that harbor a distant Shine-Dalgarno sequence from the translation start site [106]. Also, spermidine regulates the translation of transcription factors like *cra* and sigma factor *fliA,* which have an unusual GUG start codon in their transcripts [25,106]. Beyond its key role in enhancing translation, polyamines interact with the DNA and aid in supercoiling and modulate the expressions of several redox switches under oxidative stress in bacteria [105]. Their role is further exemplified in the uropathogenic *E. coli* transposon mutants of the *cadC* gene or its transcriptional targets (*cadA* and *cadB* that synthesize cadaverine), that fail to survive in an acidified nitrite medium. Further, the wild-type bacteria upregulated these cadaverine synthesis genes upon exposure to nitrosative stress [107]. Together, these studies underscore the antioxidant role of polyamines in bacterial pathogens.

During infection, *Streptococcus pyogenes* experience oxidative stress within the host macrophages. Although it lacks biosynthetic machinery for polyamines, it utilises host spermidine to survive within hostile macrophages. Spermidine upregulates the oxidative stress response genes such as *mtsABC*, *npx*, and *sodM* and virulence factors such *hasA*, *sagA*, and *slo* in *Streptococcus pyogenes* [108]. In *Streptococcus pneumoniae,* loss of spermidine transporter (*potABCD*) downregulated the *treR,* the scavenger of H_2O_2, implying an intracellular redox imbalance compromising it's *in vivo* fitness [109]. Studies also show the protective role of bacterial polyamines against bactericidal antibiotics in a few pathogens. Polyamines in *E. coli* protect from the oxidative stress generated by the fluoroquinolones, aminoglycosides and cephalosporin class of antibiotics [110]. Likewise, the surface localised spermidine in *Pseudomonas aeruginisa* prevented damage to the outer membrane in the presence of polymixin B and H_2O_2 [111]. While in *Mycobacterium tuberculosis,* deprivation of arginine decarboxylase, a key enzyme for polyamine production, impaired survival *in vivo* with concomitant high intracellular ROS and DNA damage [112]. On the other hand, extracellular polyamines have been found to enhance the efficacy of anti-tuberculosis drugs such as Isoniazid and Rifampicin by escalating intra-bacterial ROS production [113].

Intracellular pathogenic bacteria use a secretion system to inject their pathogenic islands encoded virulence effector molecule to hijack the host machinery. The Type III secretion system (T3SS) is a key virulence factor in many pathogens, including *Salmonella* and *Pseudomonas*, that aid invasion by translocating effectors into host cells. Spermidine synthesized by bacteria can regulate multiple downstream signalling inside the host cells. Pathogen's interaction with the eukaryotic host polyamines is also crucial for infection. *Salmonella Typhimurium* assembles the type 3 secretion machinery by taking advantage of the host's polyamines [26]. *Salmonella* infection also induces the expression of host genes *ODC* and *SRM*, which are involved in polyamine synthesis. Although polyamine supplementation increased *Salmonella* pathogenicity, on the other hand, *Salmonella* colonization was mitigated by the decrease in polyamine levels driven by an FDA-approved drug α-difluoromethylornithine (DFMO), which inhibits host polyamine production and induces production of nitric oxide by *iNOS* [26,104]. Correspondingly, the gastric cancer-causing *Helicobacter pylori* upregulates host polyamine oxidases to produce chronic low levels ROS in the gut epithelia. The ROS generated is well counteracted by the stealthy pathogen while initiating carcinogenesis [93]. The inhibitor of spermine oxidases (SMOX) or SMOX knock-out mice exhibited lesser DNA damage, β-catenin activation and reduced adenocarcinoma upon *H. pylori* infection [114,115]. The chronic ROS production contributes to genetic and epigenetic changes that drive carcinogenesis in infected patients. SMOX translation is controlled by *mir-124* and binds to the 3′-UTR of SMOX and inhibits the translation. The *mir-124* methylation and thereby unregulated SMOX translation are observed in the Colombian population with *H. pylori* gastric cancers [114,116]. Furthermore, Enterotoxigenic *Bacteroides fragilis* (ETBF) is a driver of colorectal cancer (CRC) in the infected hosts. It secreted a toxin that targets host cell machinery and causes DNA damage [117,118]. As a countermeasure the host cells activate the ROS production, chemokine synthesis and altered mucosal immune response that eventually contributes to CRC. SMOX activity is a prime source of the ROS accumulation, DNA damage and development of carcinogenesis [117]. Thus, it can be concluded that polyamines are essential for pathogen survival in hostile host environments characterized by excessive ROS and RNS, by regulating their gene expressions, and in some cases, that of the host genes. Besides, polyamine metabolism is a suitable target for pathogen treatment and antibiotic-resistance medication development (Fig. 2).

4.1.2. Plant hosts

Numerous cellular functions, such as the regulation of gene expression, cell proliferation, cell cycle, and cell signalling modulation, have been demonstrated to be controlled by polyamines in plants. Studies reveal the significance of polyamine biosynthesis in plant defence and

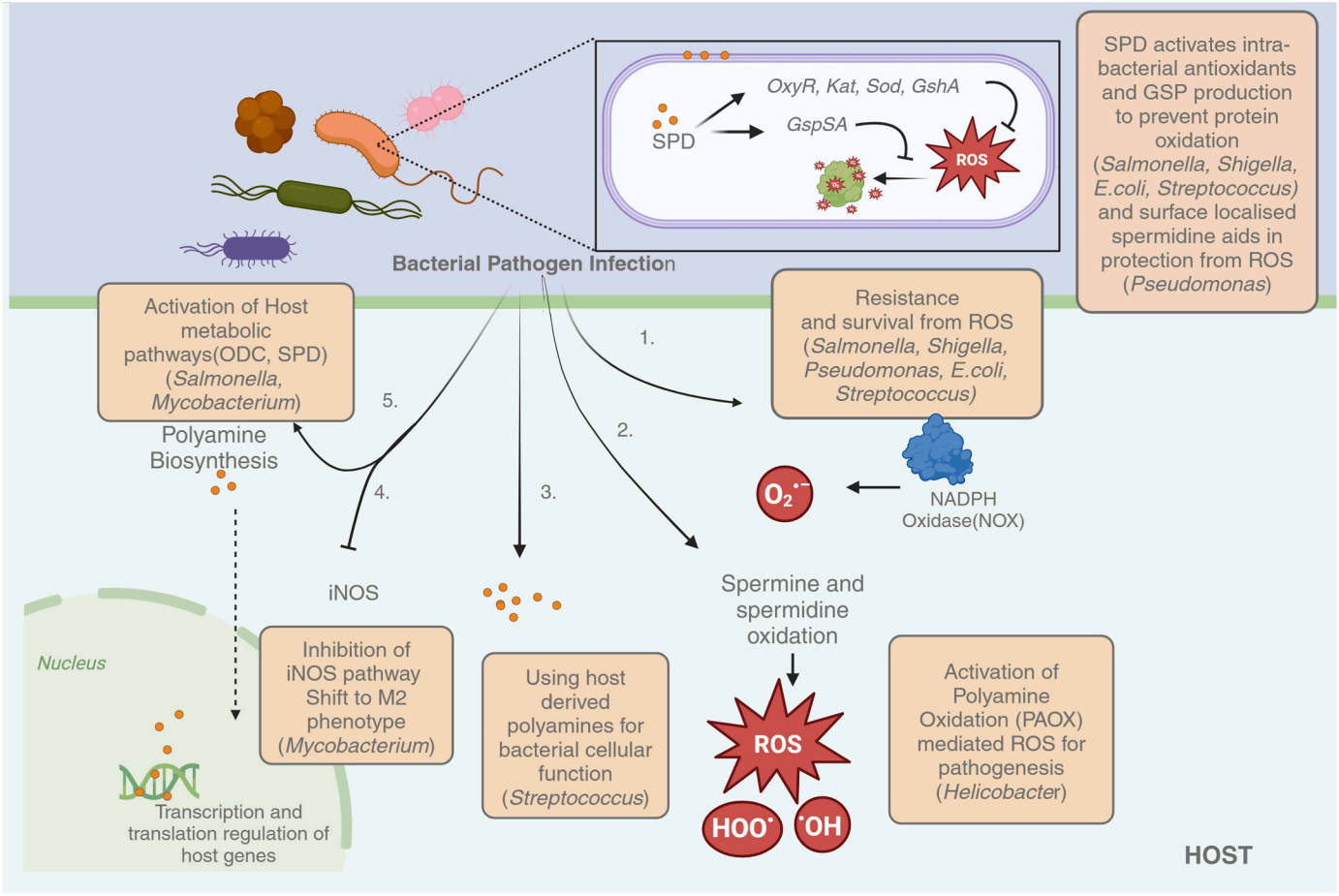

Fig. 2. The diverse role of polyamines in bacterial pathogens during their pathogenesis- Polyamines are associated with the bacterial innate defence mechanisms by either modulating their own gene expressions or host genes. They also act as quenchers of ROS and thereby aid in oxidative stress resistance in bacteria. While some bacteria upregulate polyamine oxidation and ROS production which is necessary for their disease pathogenesis. PAOX- Polyamine oxidase enzyme, ODC- Ornithine decarboxylase, SPD-spermidine, OxyR-oxidative responsive two-component system, Kat- Catalase, Sod- Superoxide dismutase, GshA- Glutathione synthase, GspSA- Glutathionyl-spermidine synthetase, NOS- Nitric oxide synthase.

plant-pathogen interactions. However, thoroughly comprehending polyamine functions in biotic stress is still elusive. Plants use particular polyamines to strengthen their immune systems, while plant pathogens use them to improve their invasion capabilities, such as through sporulation and appressorium production. Bacterial pathogens are devastating, infecting many crops and ornamental plants worldwide. *D. fangzhongdai* strain ZXC1 knockout strains of *speA* and *speC*, which encodes polyamine biosynthesis, reduced bacterial motility, decreased production of plant cell wall degradation (PCWD) enzymes, and attenuated the bacterial virulence on taro and potato. The study demonstrated that the putrescine signalling system regulates *D. fangzhongdai* virulence mainly by modulating the bacterial motility and production of PCWD enzymes [119]. Further, the deletion of the *speA* gene in *Dickeya zeae* involved in putrescine synthesis decreased the bacterial swimming motility, swarming motility, and biofilm formation, and exogenous addition of putrescine effectively rescues the defective phenotypes of *D. zeae*. It could detect and respond to putrescine molecules produced by itself or from host plants through specific transporters PotF, and the putrescine signal is critical for *D. zeae* EC1 bacterial invasion and virulence against rice seeds [120]. The exogenously secreted putrescine acts as a protector and increases tolerance of *Pseudomonas syringae* to hydrogen peroxide and also upregulates the expression of bacterial catalases [121].

Plants use an effective immune strategy during biotic stresses, amplifying cellular ROS by the catabolism of polyamines via polyamine oxidases [45]. In response to bacterial invasion, putrescine elicits an effector-triggered immunity and systemic acquired resistance by accumulating salicylic acid via ROS-dependent signalling in plants [122]. The transgenic line of *Arabidopsis thaliana* silenced in ADC genes (involved in PAs biosynthesis) with low polyamine content and high levels of ROS was more susceptible to *Botrytis cinerea*, showing more significant lesion length and a higher incidence of fungal infection. On the other hand, the ADC-silenced line showed increased resistance to phytopathogenic bacterium *Pseudomonas syringae* [123]. Also, the infection of *Pseudomonas viridiflava* in tobacco plants led to an increase in spermine levels in the leaf apoplast, and inhibitor of spermine oxidases led to higher biotrophic bacterial colonization in tobacco [124]. Furthermore, *Pseudomonas cichorii* infection resulted in the upregulation of polyamine metabolic genes and hydrogen peroxide production in tobacco as a hypersensitive response [125]. A similar hypersensitive response is also initiated by infection of *Pseudomonas syringe* in *Arabidopsis thaliana* and *Magnaporthe grisea* infection in rice plants [125]. Apart from being involved in immune response, the polyamine is a key factor regulating plant-bacteria symbiosis. The beneficial rhizobacterial strain of *Bacillus megaterium* BOFC15 induces polyamine production in the *Arabidopsis* and aids in stress resistance. Similarly, the symbiotic relationship between the rhizobacteria *Sinorhizobium meliloti* and legume *Medicago truncatula* largely depends on polyamine oxidases in the host plant [126]. At the host-pathogen interface, polyamines are secreted by both plants and pathogens during plant-pathogen interaction. While pathogens produce certain polyamines to increase their pathogenicity, plants secrete polyamines as a defense strategy. The

result is uncertain because both the pathogen and the plant can use the released polyamines [127] (Fig. 3).

4.1.3. Other hosts

In the invertebrate sea cucumber *Apostichopus japonicus,* nitric oxide is produced by *iNOS* upon bacterial invasion. The major pathogens of marine organisms *Vibrio splendidus* and *Vibrio parahaemolyticus* infection in *A. japonicus* result in a metabolism shift from polyamine biosynthesis to nitric oxide production by *iNOS* activation [128]. Besides, the deep-sea tube worm *Riftia pachyptila* depends mostly on the symbiont bacteria for nutrition as it lacks a digestive system. A recent transcriptomic study showed that *Riftia* does harbour polyamine biosynthesis genes, however, the polyamines spermidine and spermine play a significant role in their symbiotic relationship, which may be more than just a source of nutrition [129]. On the other hand, the host *Riftia* protects its bacterial symbionts which populates the trophosome, from oxidative damage, with elevated levels of ROS detoxifying genes SODs and peroxidins [129] (Fig. 3). Polyamines also act as nutritive chemosensory molecules that attract *C. elegans* to its nutritive food source. Spermidine and putrescine from *E. coli* elicit a neural circuit via the AIB interneurons in these worms to direct the movement of *C. elegans* towards the nutritive bacteria while keeping them drifting from pathogenic *Enterococcus faecalis* [130]. Collectively, polyamines are essential mediators of host-microbe interactions across diverse invertebrates, influencing immune responses, symbiotic relationships, and behavioral adaptations. Their roles in metabolic shifts, oxidative stress protection, and chemosensory signaling highlight their significance in maintaining host health and microbial balance.

4.2. Virus-host interactions

4.2.1. Animal and human hosts

The presence of polyamines in viruses was first explored in bacteria infecting bacteriophages. The bacteriophages were critical models for studying the role of polyamines in viral infection and pathogenesis. Early studies in the 1970s showed the packaging of about 1000 polyamine molecules in virions to neutralise the negative charge of the nucleic acids in them and its compaction [131]. Apart from neutralising, polyamines in bacteriophages have also been shown to be critical for virion packaging using polyamine-depleted *E. coli* K 12 strain [132]. The first study of polyamines in the human virus was in Herpes Simplex Virus-1 (HSV-1) with the observation of spermine and spermidine in the viral nucleocapsid and envelope, respectively [133]. The human cytomegalovirus (HCMV) enhances polyamine metabolism in the host cells for its uptake [134]. Polyamines are linked to viral replication, survival and pathogenesis during infection. Polyamines are conventionally considered to be ROS-scavengers, while their catabolism releases ROS by the action of oxidases. The relationship between polyamines and ROS is complicated and contextual during pathogen infection. In some cases, ROS is beneficial to the pathogen, while in others, it negatively impacts the survival in the host.

In the case of the Hepatitis C virus (HCV), a vital step in its pathogenesis is boosting ROS production by induction of several ROS-generating enzymes in the host cells [135,136]. HCV infection in Huh7 cells led to decreased levels of spermidine and spermine, low expression of polyamine biosynthesis genes and high expression of polyamine catabolism genes such as polyamine oxidase and SMOX via its core and NS5A proteins [137]. It also led to overall decreased polyamine levels in the host cells and high levels of ROS. Higher ROS correlated to higher HCV-driven liver cirrhosis and carcinogenesis [136]. The inhibition of polyamine biosynthesis and associated oxidative stress pathways attenuated Influenza A virus (IAV) survival in THP1 cells [138]. Also, the Porcine epidemic diarrhea virus (PEDV), which is a cause of fatal viral infection in swine, upregulated the host spermine oxidase and acetyl polyamine oxidase enzymes upon infection into Vero cells. These enzymes catalyse the interconversions of spermidine and spermine, generating ROS [139]. At the same time, HIV-1 cause neuronal toxicity in human neuroblastoma cells by stimulating spermine oxidase, production of ROS and other byproducts via HIV-1 Tat protein [140]. HIV-1 infection is often associated with cognitive disorders like dementia, and Capone et al. hinted at the role of polyamines in HIV-1 neuropathogenesis [140]. On the contrary, another study suggested that in the case of Human Immunodeficiency Virus type-1 (HIV-1), the amine oxidase system shows potential antiviral activity by the release of hydrogen peroxide from spermidine and spermine in the semen and vaginal canal [141]. Thus, polyamines like spermine and spermidine are

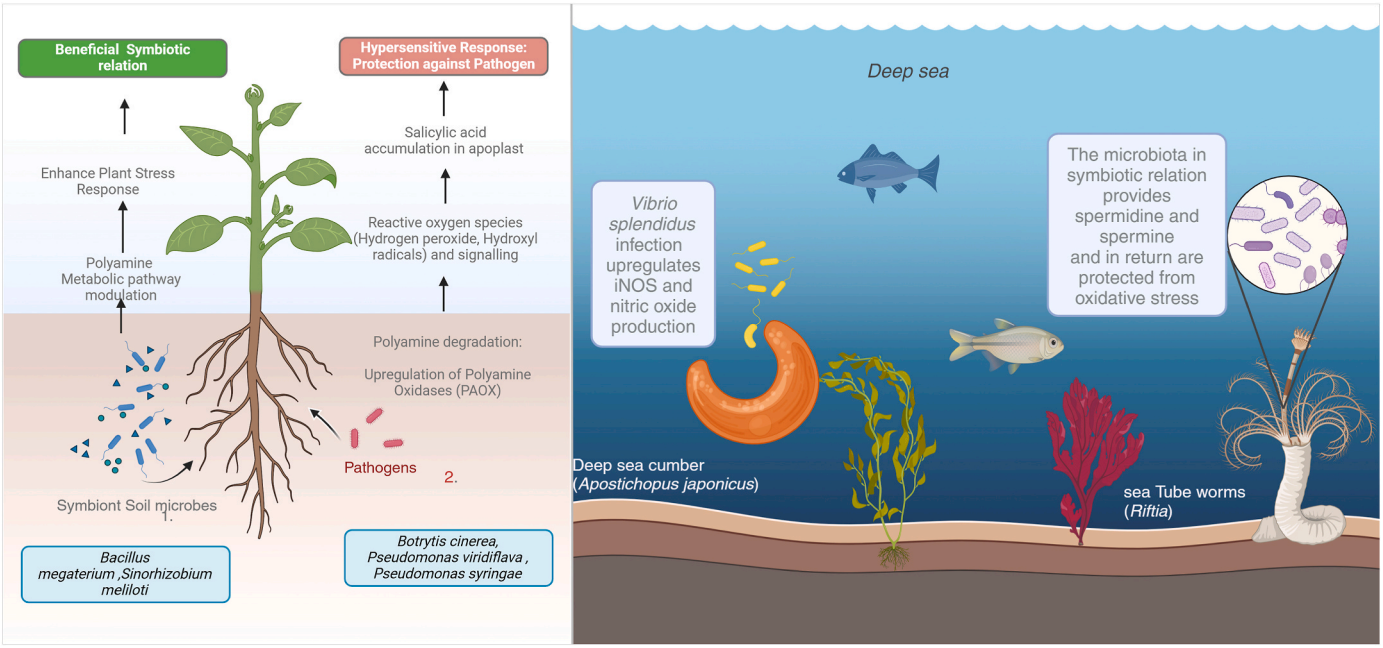

Fig. 3. ROS and polyamines are essential in the interactions between pathogenic and symbiotic bacteria and their hosts - In plants, polyamine metabolic pathways are modulated in response to pathogenic bacterial infection to mount a hypersensitive reaction, while the symbionts regulate host pathways and mediate beneficial host-bacteria relationship. Polyamines and ROS are key players in the interactions between invertebrate hosts and bacteria. NOS- Nitric oxide synthase.

one of the causes of the generation of ROS and ROS-associated species during viral infection in animal hosts, which acts as a boon for the viruses. The role of these cationic molecules in the host-virus interplay is partially connected to ROS generation apart from their vital function in viral genome replication and packing.

Some viruses depend on polyamines during infection of the host. The EBOV, CHIKV and ZIKV rely on spermidine-mediated hypusination of host translation elongation factor eIF5α for viral protein translation [142]. Coxsackievirus B3 (CVB3) requires polyamines in several steps of its infection cycle and adapts stealthily to polyamine depletions by the host upon CVB3 infection. The V3 capsid protein of CVB3 undergoes mutation Q234R in polyamine-depleted conditions, which renders it invasive even in the absence of polyamines [143]. Moreover, its proteases 2A and 3C also undergo mutations during polyamine depletion and aid in cleaving the host proteins [144]. Thus, host cells regulate the polyamine production upon virus entry to limit the infection. Besides, the interferon-stimulating genes (ISG) are upregulated upon viral infection, which targets SAT1 through interferon α/β. SAT1 is a major inhibitor of ODC1 and polyamine biosynthesis [145]. Polyamines play a crucial role in viral infection and pathogenesis, facilitating viral genome packaging, replication, and host adaptation. Their interplay with reactive oxygen species (ROS) can either enhance or hinder viral survival, highlighting their dual role in both promoting infection and serving as potential antiviral targets (Fig. 4).

4.2.2. *Plant hosts*

The role of ROS and related species in plant-virus interaction is widely studied, where ROS plays a critical role in pathogen restriction and is also a signalling molecule that elicits a defense response [146,147]. Infection of plants with the virus leads to a cascade of events, which eventually causes a burst of ROS both locally and in other major plant organs [148,149]. The ROS generated locally acts to kill the infected viruses, while globally, it also helps the plant to adapt to viral infection [150,151]. The destruction of tomato plants is often due to infection with the tomato mottle mosaic virus (ToMMV), which leads to mottling symptoms. Nagi et al. showed that infection of ToMMV in *Solanum pimpinellifolium* induced Nitric Oxide(NO°) production while decreasing polyamine biosynthesis [152]. The results can be justified by understanding arginine metabolism, the common precursor for polyamines and NO°. Infection of the Cucumber mosaic virus (CMV) into *Arabidopsis thaliana* significantly stimulated the expression of spermine-responsive genes in the host tissues. CMV infection triggered *ZAT7*, *ZAT12* and *AtWRKY40* transcription factors, which are members of the hydrogen peroxide signalling pathway in *A. thaliana [*153*]*. These expression profiles were reverted upon treatment with inhibitors of the Spermine oxidase enzyme, which generates hydrogen peroxide by oxidation of spermine. Moreover, the inhibitor led to higher CMV loads in plant tissues [153]. Another study revealed that thermospermine (T-Spd) controls the multiplication of CMV in *A. thaliana* by activating spermine-responsive genes and ROS signalling pathway genes [154]. T-Spd activated mRNA expression of mitochondrial Alternative oxidases (*AOX*) and pathogen defence-associated hydrogen signalling cascade transcription factors such as *ZAT7, ZAT12, NR, RAN1* etc [154]. During infection of Tobacco mosaic virus (TMV) in tobacco cultivars that show resistance to TMV, polyamines have been found to be one of the sources of hydrogen peroxide during plant hypersensitive reactions [155,156]. Furthermore, the burst of ROS provides a symptomless resistance against Potato virus X during infection in *Nicotiana tabacum* (tobacco plants) [157]. Polyamines serve as one of the primary defence-associated molecules during pathogen invasion in plants. The mechanisms involved in such processes often includes miRNAs, viral proteins, and also host protein factors. The miRNA-167 in maize targets ARF30 transcription factor for degradation. ARF30 functions to bind to the promoter of Polyamine oxidases (*PAOX*) and activates the *PAOX* expression. Interestingly, the Maize chlorotic mottle virus, activates the *PAOX* gene transcription. Thus, miRNA-167 is employed by the maize plant upon infection with MCMV to prevent *PAOX* expression and control the viral infection [149]. In other instances, certain viral proteins are recognised by the host and, in turn, trigger a defence mechanism, majorly through the generation of ROS. The p33 protein of the *Citrus tristeza* virus triggers the activation of host ROS generation, restricting the virus entry into the phloem [158]. Similarly, a study shows that infection of maize plant with the Sugarcane mosaic virus (SMV) leads to differential regulation of several host genes. The genes include the polyamine oxidases, and inhibition of this enzyme promotes viral pathogenesis. The study suggested that polyamine oxidases are activated to generate ROS and restrict SMV infection [159] (Fig. 4). Hence, polyamines play a pivotal role in plant-virus interactions by modulating

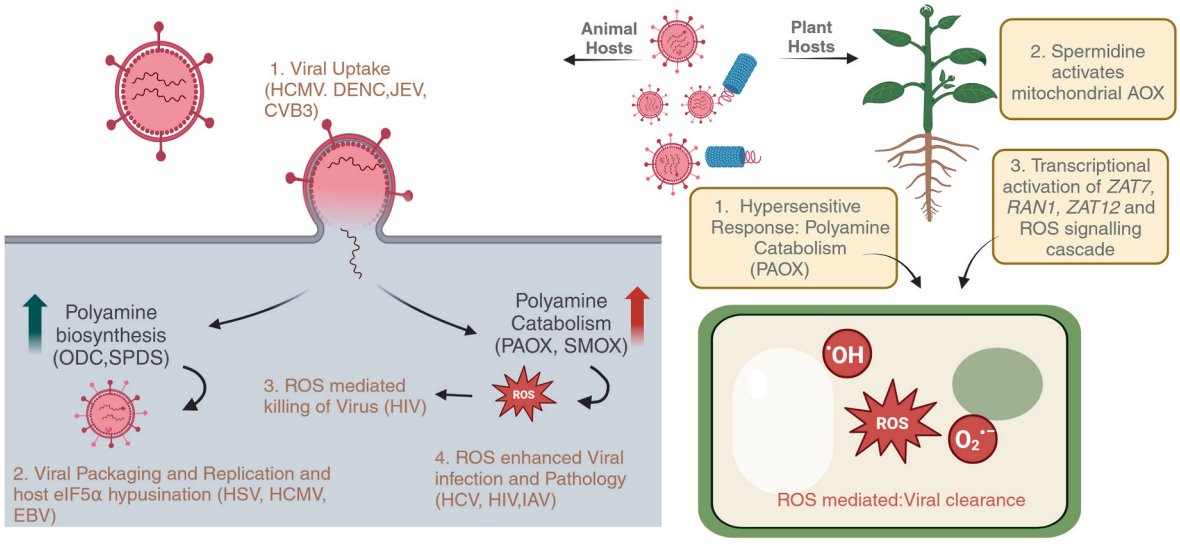

Fig. 4. Viral-host interaction involves polyamines and oxidative stress interplay during infection in hosts- In animal and plant hosts, viruses utilize the host machinery to generate higher polyamine for viral survival and ROS for viral disease pathology and spread. Virus infection in plants activates plant immune response involving polyamine oxidation and ROS signalling for viral clearance. AOX- Alternative oxidases, PAOX- Polyamine oxidases, HSV- Herpes Simplex Virus, HCMV- Human cytomegalovirus, DENV- Dengue virus, JEV- Japanese encephalitis virus, EBV- Ebola virus, HIV- Human Immunodeficiency virus, HCV- Hepatitis C virus, IAV- Influenza A virus.

ROS production, which can either enhance plant defense or influence viral pathogenesis. Their regulation through transcription factors, miRNAs, and viral proteins highlights their significance as key molecular players in plant immune responses.

4.3. Protozoa-host interaction

4.3.1. Human hosts

Protozoan diseases such as Chagas disease, Leishmaniasis and malaria are common in the tropics and have been classified as neglected tropical diseases by the WHO. However, they remain a significant problem worldwide due to travel and immigration. The disease occurrences show a positive correlation with immunocompromised conditions, such as with patients suffering from acquired immunodeficiency syndrome (AIDS) [160,161]. The Trypanosomatids have unique structural components, including a kinetoplast, a single mitochondrion and a layer of glycocalyx on the plasma membrane. They also encounter an array of stressful conditions during their life cycle. These protozoans harbour a specialised molecule, Trypanothione ($T(SH)_2$), a major stress-resistance molecule during infection into the host and life outside the host [162]. Unlike higher eukaryotes, these protozoans have evolved to express the trypanothione synthetase enzyme, which conjugates two glutathione molecules to a single spermidine molecule and generates trypanothione [162,163]. The trypanothione and trypanothione reductase replace the glutaredoxins (Grx) and thioredoxins (Trx) present in the other eukaryotes to regulate redox homeostasis [163]. Bacteria, on the other hand, harbor the enzyme Glutathionyl spermidine synthetase, which serves as an antioxidant among multiple other antioxidant enzymes. In kinetoplastids, T(SH)2 is the most critical antioxidant enzyme, which is essential for infection into the host. During infection into the host, the host immune system is triggered to produce a burst of reactive species such as the superoxide radical ($O_2^{\circ-}$) and hydrogen peroxides [164,165]. The parasite takes countermeasures to sustain the attacks of the generated ROS and strategically utilises the host resources to facilitate its growth in the host environment [164,166]. *Trypanosoma cruzi* and *Trypanosoma brucei* the causative agents of Chagas disease infect the host macrophages where they come across ROS generated by the NADPH oxidases [167]. However, the potent antioxidant property of trypanothione aids in quenching ROS and prolonging parasite persistence, leading to chronic inflammatory stress in Chagas disease [167]. The Trypanothione synthetase (TryS) enzyme is critical in imparting survival advantage in *T. cruzi.* The inhibition of this enzyme in *T. cruzi* led to attenuated survival and poor resistance to oxidative stress and heavy metal toxicity. While the overexpressing TryS in *T. cruzi* resulted in a higher resistance and proliferation. The over-expression also aided in tolerating benznidazole and nifurtimox, which are commonly used drugs for the treatment of Chagas disease [168].

Leishmaniasis is another protozoan parasitic disease which is widely spread worldwide [169]. This disease has three major clinical forms: visceral leishmaniasis, cutaneous leishmaniasis and mucocutaneous leishmaniasis. The first step to the disease is infection by the pathogen. The tissue-resident macrophages and infiltrating neutrophils are the major immune cells encountered by this pathogen. Neutrophils tend to control the spread of infection from the site by their phagocytic and enzyme/antimicrobial-protein mediated killing of the protozoa and forming the Neutrophil Extracellular Traps (NET) [170]. *Leishmania* spp. possess the 3′-Nucleotidase activity to degrade the NET, and higher *Leishmania* nucleotidase activity was correlated to the clinical manifestations in Leishmaniasis patients [171]. Furthermore, they utilize macrophages to survive and cause a long-lasting patient infection [172]. Although macrophages provide a toxic environment with NADPH oxidase (NOX2) and NOS2 mediated ROS and RNS production, and low pH, *Leishmania* spp. have evolved robust strategies to survive within the macrophages and cause infection [173–176]. In patients with diffused cutaneous leishmaniasis (DCL) caused by *L. amazonensis*, the skin lesions showed elevated expression of polyamine enzymes and transporters, suggesting the role of polyamines in the disease phenotype of tegumentary leishmaniasis [177]. *Leishmania* spp. also generates trypanothione from spermidine and glutathione to restrain the host cells' oxidative stress, which serves as the major antioxidant in these species and are the potential targets to generate anti-leishmanial drugs [178]. Hypericin, a natural compound and inhibitor of *Leishmania* spermidine synthase, was found to reduce the trypanothione levels in *L. donovani* and generate high ROS levels, resulting in the death of *Leishmania* promastigotes [179]. The enzyme ornithine decarboxylase (ODC), which catalyses the rate-determining step of the polyamine biosynthesis pathway, serves to protect against the host immune system. The recombinant enzyme from *Leishmania donovani* (r*ld*ODC) dampened the Th1 immune response in visceral leishmaniasis (VL) patients by upregulating IL10 production and suppressing IFNγ from the $CD4^+$ T cells [180]. Moreover, r*ld*ODC led to very low levels of NO and ROS production in VL patients, which was rescued upon treatment with an ODC inhibitor, further shedding light on the predominant role of polyamines in *Leishmania* pathogenesis [180].

L. donovani secretes exosomes, which contain high levels of polyamines and are readily internalised by the host macrophages. This causes enhanced phagocytic activity and uptake of the parasites by macrophages [181]. The exosomes containing polyamines modulate the host macrophage to the anti-inflammatory M2 phenotype, with high Arginase1 and low NOS2 activity. Also, boosts solute carrier transporter (SLC3A2) activity to increase the spermidine levels and thus maintain an anti-inflammatory environment [181]. Furthermore, another group explained that *L. amazonensis* utilises miR-372, miR-373 and miR-520d to reprogram the polyamine biosynthesis in THP-1 derived macrophages to favour the parasite survival and protection against host stress [182]. Apart from modulating the host metabolic pathways during infection, the parasite also rewires its own metabolic pathways under oxidative stress. Under *in vitro* oxidative stress, *L. donovani* shifts the metabolic flux from glycolysis to the pentose phosphate pathway and maintains the $NADPH:NADP^+$ ratios to sustain the intracellular reduced thiols [183]. Also, recent studies have shown that spermidine synthase enzyme knockout in the malarial parasite *Plasmodium yoelli* caused significant defects in the blood-borne stages of malaria infection [184]. Furthermore, spermidine is a vital metabolite for intracellular survival of the parasites, *Babesia duncani* and *Plasmodium falciparum* [185]. On the other hand, the hosts utilize polyamines to counteract the invading protozoan parasites by employing polyamine oxidases to generate ROS and cause intra-erythrocyte killing of multiple *Plasmodium falciparum* isolates [186]. While, infection of *Trichomonas vaginalis* results in the production of vaginal discharge, which is shown to consist of high levels of polyamine putrescine [187]. This protozoan parasite synthesises putrescine, secretes it into the discharge, and, in turn, antiports spermine from the host milieu [188]. A study presented that the inhibition of intracellular putrescine in *T. vaginalis* resulted in alterations in the proteomic profile of this pathogen, with downregulation of multiple pathways, including the redox homeostasis pathway [188]. Furthermore, this sexually transmitted disease in humans is due to infection with *T. vaginalis* and *Tritrichomonas foetus*, which is treated by metronidazole-mediated ROS/RNS production [189,190]. Recently, a group showed a higher killing efficacy of a diamine compound that blocks polyamine pathways in this pathogen without producing ROS [191]. (Fig. 5). In conclusion polyamines play a critical role in protozoan pathogenesis by aiding parasite survival through antioxidant mechanisms, immune modulation, and metabolic reprogramming.

4.3.2. Other hosts

Vibrio cholerae, the causative agent of cholera in humans, thrives in aquatic systems, and it is required to protect and survive from the predation of bacterivorous protists such as *Acanthamoeba castellanii.* M. M Hoque et al. found a mechanism that allows *V. cholerae* to survive within its protozoan hosts and showed that the bacterial flora mutant upregulated iron acquisition, amino acids biosynthesis and oxidative stress

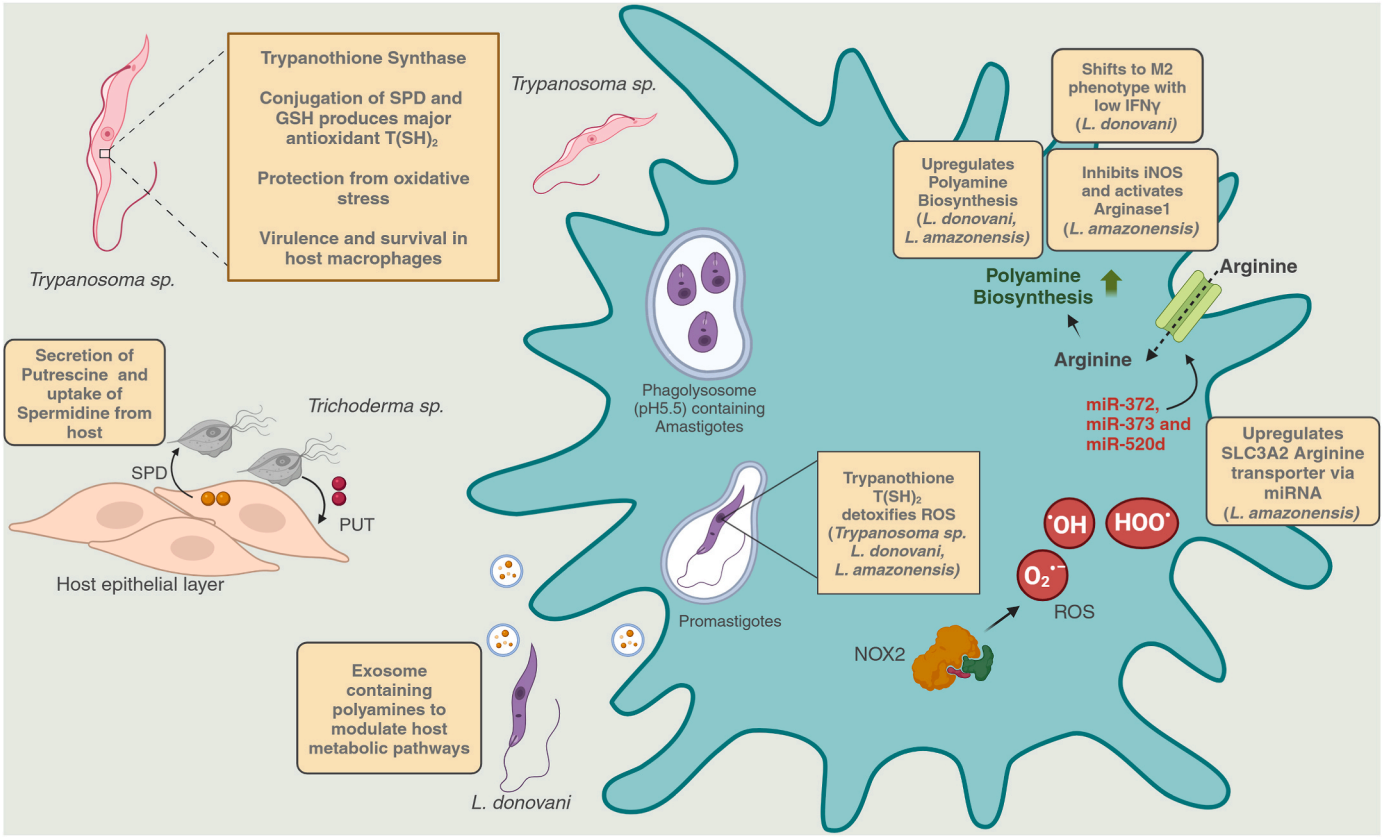

Fig. 5. Protozoa and host interactions are influenced by polyamines - Human protozoan pathogens majorly depend on polyamines synthesized de novo or acquired from host cells for their survival and antioxidative responses during infection. Protozoan pathogens alter host gene expressions by regulating host miRNAs. They rely entirely on Trypanothione, a key protozoan antioxidant, for their antioxidative stress responses. T(SH)2 – Trypanothione, NOX- NADPH oxidase.

genes upon infection into the *A. castellani* [192]. While highest upregulation was seen in arginine metabolism, a common precursor to essential metabolites such as polyamines and glutamate [192]. Polyamines and reactive oxygen species (ROS) play a dynamic role in host-pathogen interactions, extending to other microscopic hosts.

4.4. Fungi-host interactions

4.4.1. Human hosts

There is a highly complex and dynamic relationship between the fungus and its diverse host, arising from the evolution of large numbers of fungal pathogens, the host niches they occupy and the immunity from the host. Adaptation of the fungal pathogens with the constantly changing host microenvironments set up the dynamic fungus-host interactions. These organisms are ubiquitous, and a few are associated with humans and plants, causing diseases [193]. The WHO has also published a Fungal pathogen priority list (FPPL) in the year 2022 and has enlisted the critical, high and moderate priority invasive fungal pathogens that cause morbidity and mortality worldwide [194]. Only a few fungal pathogens are considered true pathogens, able to infect and invade their hosts. In contrast, others are opportunistic pathogens and depend on poor immunity or loss of immune barriers to invade and infect the host [195]. The environmental challenges, both within and outside the host, require the fungal pathogens to adapt rapidly by altering multiple gene expressions. These organisms have conserved genes, including the carbohydrate, protein metabolic pathway genes, antioxidant and ROS stimulated genes, etc. The investigations of polyamine metabolic pathways in fungi suggest the critical role of these cationic molecules in fungal stress responses [196–198]. The *spe2* mutant of *Saccharomyces cerevisiae* that does not synthesize spermidine and spermine showed cessation of growth under high oxygen levels [199]. Further, a follow-up study showed that in *spe2* mutants, there is intracellular ROS accumulation when grown aerobically [200]. In the opportunistic human pathogen *Penicillium marneffei* infecting immunocompromised individuals and with a travel history from southeast Asia, a mutation in the S-Adenosylmethionine decarboxylase that catalyses spermidine synthesis resulted in poor conidia formation and germination. Since inhalation of conidia is a prerequisite for infection, the study suggested that spermidine biosynthesis in this pathogen might be a potential target for combating infections [201]. Furthermore, the assessment of polyamine metabolism in another opportunistic pathogen, *Emergomyces africanus,* revealed the high expressions of ornithine decarboxylase and agmatinase, with intracellular low putrescine levels and high spermidine levels and polyamine-mediated dimorphic switching in this yeast [202]. This suggested the importance of spermidine in cellular functions, most importantly in oxidative stress regulation.

Cryptococcus sp. are other members of the opportunistic human fungal pathogens causing meningitis and death in immunocompromised humans [203]. Recent studies indicated that the urease-deficient *Cryptococcus neoformans* were defective in polyamine and arginine metabolic pathways and led to decreased melanin production and higher levels of intracellular ROS [204]. Urease is a cryptococcal virulence-associated gene vital for blood-brain barrier traversal, increasing the phagolysosomal pH and survival within the host macrophages and alkalinisation by release of ammonia to cause host tissue damage [204]. Another study previously showed that *C. neoformans* spermidine synthase mutants are impaired in melanin production, a key virulence determinant of this pathogen [205]. Corroborating from these, spermidine is a molecular player modulating the intracellular processes to aid in the pathogen survival via its complex and dynamic interactions with several virulence genes, such as the urease. Another study reported the

effective killing of *C. neoformans* but not *Candida albicans* nor *Aspergillus fumigatus in vitro* by the polyamine oxidase system [206]. Oxidation of polyamines spermidine and spermine by polyamine oxidases produces reactive species such as hydrogen peroxides and acrolein, which show antifungal activity against *C. neoformans* [206]. *Candida* sp. is another critical group of fungal pathogens infecting immunocompromised humans. The widely used polyamine biosynthesis inhibitor D, L-α-diflouromethylornithine (DFMO) shows growth inhibition of pathogenic isolates of *Candida albicans, Candida tropicalis* and *Candida parapsilosis* [207]. The use of spermidine synthase inhibitor Cyclohexylamine with DFMO showed a higher antifungal effect *in vitro*, which was further enhanced by using spermidine analogue Triamine 4–8 [208,209]. With the need to develop more potent and effective anti-fungal drugs, Mangiferin, a xanthone isolated from mango fruit, when administered with Caspofungin(CG), a commonly used anti-fungal drug, enhanced the antifungal activity of CG by destroying *C. albicans* biofilm and clearing pathogen in BALB/C mice [210]. Mangiferin, combined with Caspofugnin, inhibited *SPE1* expression, increased oxidative damage, and led to fungal cell death [210]. Further, polyamine biosynthesis inhibitors DFMO and 1,4-diamino-2-butanone (DAB) amplified the anti-biofilm activity of amphotericin B against *C. albicans* biofilm. The combination of the inhibitors and amphotericin B shoots up the ROS in biofilm cells via escalating *CamCA1* caspase activity, leading to oxidative damage and fungal killing [211]. Thus, polyamines contribute to fungal survival by regulating oxidative stress, promoting virulence factors, and enabling morphological transitions. Meanwhile, ROS, generated through polyamine metabolism or host immune responses, can either aid fungal persistence or serve as a host defense mechanism. (Fig. 6).

4.4.2. Plant hosts

Greenland and Lewis were the first to show the alterations in plant polyamine metabolism upon infection with a fungal pathogen. They observed that rust infection of the biotrophic fungal pathogen *Puccinia hordei* in barley plants increased leaf spermidine levels [212]. Further, Walters and Wylie reported the enhanced expression of polyamine metabolic genes such as ODC and ADC in the area surrounding the fungus pustule on the barley leaves upon infection with powdery mildew fungus *Blumeria graminis* f. sp. *hordei* [213]. Since then, numerous research studies have focused on understanding the role of polyamines in fungal-plant interactions. *Ustilago maydis* a dimorphic biotrophic fungal pathogen and causes the common smut disease in maize plants, resulting in tumours on the leaf blades. A study has shown that *U. maydis* infection in maize causes an increase in polyamine metabolism in the tumours and plant tissues surrounding the tumours during the early stages of plant infection [214]. Of the multiple fungal-plant interaction studies, several studies have presented the involvement of ROS and polyamines in such interactions. The beneficial Arbuscular mycorrhizal (AM) symbiont augments the polyamine metabolism in the host plants. This polyamine metabolism enhances the ability of the host to combat ROS and prevent chlorophyll damage [215]. Furthermore, a recent study revealed the favourable role of soil Arbuscular Mycorrhizal Fungi

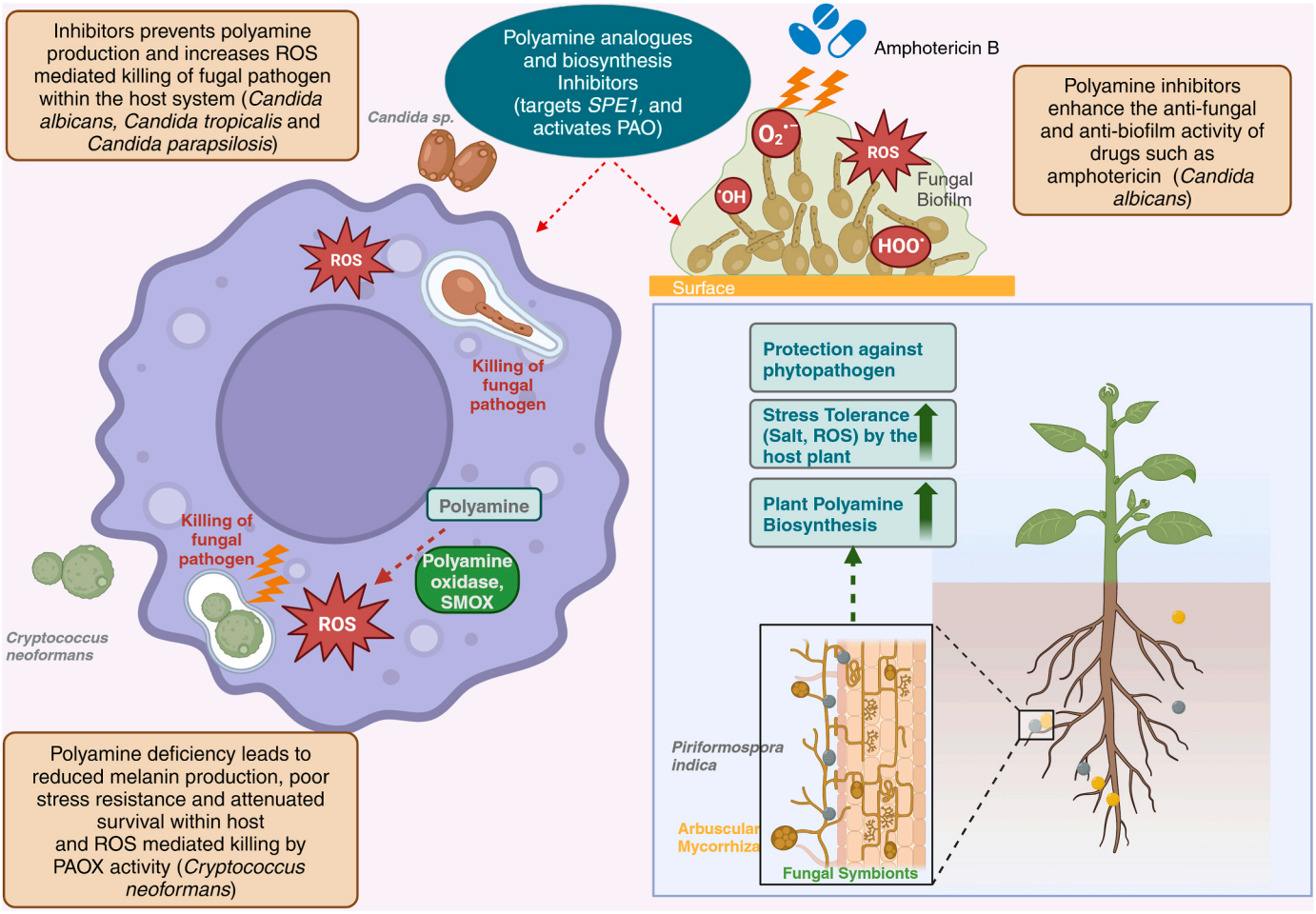

Fig. 6. Interactions between pathogenic and symbiotic fungi and their diverse hosts influence fungal behaviour and host responses- Fungal pathogens depend on polyamines to adapt and thrive within the harsh environments of the host during infection, using them to enhance survival, facilitate proliferation, and overcome the host's immune defences. The beneficial soil fungi symbiosis with host plants regulates plant responses to phytopathogens and stresses.

(AM) in the tolerance of host plants under soil moisture deficit stress (SMDS). The colonization of AM to the roots of trifoliate orange led to high levels of polyamines and polyamine precursors and high polyamine synthase activity in plants exposed to SMDS [216]. While a lower degree of membrane lipid peroxidation and low levels of reactive oxygen species in the roots [216]. Also, the endophytic fungus *Piriformospora indica* displayed a protective role against crown rot of wheat plants caused by *Fusarium pseudograminearum.* The protective effect of the *P. indica* was found to be linked to polyamines and nitric oxide. Additionally, *P. indica,* when applied to bean plants along with thiamine, reduced the disease progression of phytopathogen *Rhizoctonia solani* in bean plants [217]. *P. indica* application led to decreased accumulation of hydrogen peroxide, superoxide anion and iron in the leaf discs while increasing the levels of putrescine, spermidine and spermine, indicating the beneficial role of the endophytic *P. indica* [217] (Fig. 6). The dynamic interplay of ROS and polyamines shapes the outcomes of infections and symbioses, making them crucial targets for disease management and therapeutic strategies.

5. Boon and bane: microbiota and polyamine in modulating microbial pathogenesis

Humans share a mutualistic relationship with diverse and numerous microorganisms, known as the microbiome. Over the past two decades, studies have discovered multiple facets of the host-microbiome interactions [218,219]. The resident microbiota has evolved strategies to use up the metabolites produced by the host or released into the gastrointestinal tract [220]. Apart from using the host-derived metabolites, the microflora regulates several host functions such as immune responses, nutritional responses, digestion, etc [218]. One of the critical roles of the resident microbiota is to form an immune barrier at the gut mucosa and provide protection from invading pathogens [221–223]. The pathogens compete with the gut flora to attach and colonise the epithelial lining and infect the host tissues. A dysbiosis of the gut is connected to the development of various diseases such as obesity, cancer, and infections.

Research has bloomed over the past two decades to unravel the mysterious roles of the gut microbiome. One of the critical functions of the gut flora is its interaction with the pathogen and regulation of infectious disease pathogenesis [224]. Obesity and Type-2 diabetes increase the risk of infection and post-infection pathologies such as osteomyelitis. Oligofructose feeding of mice led to the expansion of *B. pseudolongum* in the gut and increased the polyamine contents in the caecum [225,226]. Another study parallelly showed the bifidogenic diet (oligofructose) led to a decrease in *S. aureus* in infected bone and tissues of Type-2 diabetes mice models [227]. Also, supplementation of spermidine in the diet showed a negative correlation with obesity. This was partly due to an increase in the *Lachnospiraceae NK4A136* group in the gut and enhanced gut barrier function [228]. All of them highlight the potential pre-biotic role of spermidine in enhancing mucosal barrier functions and prevention of infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection alters the gut flora with elevated *Bacteroides* and reduced *Firmicutes.* Under the same conditions, spermidine levels were found to be low, while supplementation of spermidine in the drinking water of the mice relieves the MRSA bloodstream infection [229]. The authors show spermidine drives the M2 polarisation of macrophages with low IL-6 and TNFα and high levels of IL-10 and protects from MRSA infection [229]. Some bacteria, like *Helicobacter pylori*, promote polyamine metabolism in the host tissues, which is critical for their pathogenesis and is a pre-requisite for *H. pylori* associated gastric cancer. A study shows that *Lactobacillus brevis* administration to *H. pylori* positive patients negatively regulated polyamine biosynthesis by decreasing ornithine decarboxylase activity and reducing intragastric *H. pylori* load [230]. Furthermore, faecal microbiota transplant (FMT) from donors having 80 % relative abundance of the *Bacteroides* and *Firmicutes* to *Clostridium difficile* infection (CDI) patients led to increased faecal putrescine, spermidine and butyrate levels with decreased immune activation promising a cure for CDI [231]. In HIV-infected patients, the gut flora and metabolites were altered with high putrescine and cadaverine in pre-AIDS and AIDS groups compared to the control. The pre-AIDS and AIDS group showed high levels of *Lactobacillus* and few pathogenic bacterial genera such as *Pseudomonas* and *Enterococcus*. Such alterations were correlated to immune activation and microbiota translocations, indicating to affect the mucosal barrier disruption during HIV infection [232]. Furthermore, probiotics produce spermidine, which stimulates intrahepatic $IFN\gamma^{+}$ $CD4^{+}$ T cell immune response, inhibiting Hepatitis B virus replication [130]. Besides the gut, the oral cavity harbours the second-largest diverse microbiota, and the latest research correlated the levels of spermidine, ornithine decarboxylase activity and *Streptococcus* bloom in the oral cavity during the clinical conditions of gingivitis to periodontitis. The study also showed a change in the diversity and abundance of the oral microbiota in the oral disease conditions. Authors suggest that the correlation explains the interrelations of polyamines, microbiota and *Streptococcus* in such clinical conditions. Together, these studies underscore the harmful as well as beneficial roles of the microbiome and polyamines interplay during pathogen infection.

6. Conclusion: therapeutics and future perspectives

With the advancement in the scientific field and research, understanding the vital functions of polyamines has progressed. These polycationic molecules serve as the elixir of life with their involvement in diverse physiological and cellular processes [233]. The polyamines are found to decrease with age and are linked to multiple pathologies and disease conditions in humans as well as plants [234,235]. The molecules are ubiquitously present in all organisms, from archaea to eubacteria to mammals. In every organism, they are critically associated with numerous functions, such as transcription, translation, cell division, protein interactions, etc [236,237]. Microorganisms such as the Proteobacteria and protozoans can synthesize special thiol molecules with Glutathione and spermidine, which is a key antioxidant and is essential for survival under oxidative stress conditions [238]. However, the roles of these molecules and their interplay with other molecular players, such as ROS, are complex. As Paul Nurse explains, life is a complex system and urges us to describe the complexity of the living system and then try to understand the complexity of it [239]. Similarly, the interplay of polyamines, ROS, host, pathogen and microbiota remains complex, with significant gaps in our knowledge. Future research must unravel the complexity of such interactions, molecular players, signalling networks, and cellular processes.

Nevertheless, the studies in this field have enhanced the comprehensive understanding of polyamines and the design of drug and therapeutic strategies for combatting dreadful infections and disease pathologies. With the discovery of ornithine decarboxylase(ODC) as the rate-limiting enzyme in polyamine biosynthesis, inhibitors of ODC were the first class of molecules to be used as a therapeutic strategy for curing infections and other non-communicable pathologies [240]. ODC has been the key target for pharmacological interventions to treat human trypanosomiasis, Chagas disease, and leishmaniasis. The most commonly used drug, D,L-α-difluoromethylornithine (DFMO), is promising in the treatment of protozoan diseases by targeting the protozoan thiol and polyamine pathway, which is critical for their survival within the host macrophages [241,242]. Furthermore, combinatorial treatments of polyamine transporter inhibitors such as Pentamidine along with DFMO show increased anti-trypanosoma activity [42]. At the same time, diamines have also shown a promising role as an anti-*Trichomonas vaginalis/foetus* activity over metronidazole by blocking polyamine biosynthesis [191]. Further, the novel synthetic spermidine analogues such as N1,N7-bis (3-(cyclohexylmethylamino) propyl) heptane-1, 7-diamine tetrabromide was found to be an effective anti-malarial drug by inhibiting the *Plasmodium falciparum* growth and infection

with IC_{50} of 200 nM [243]. Research has also paved the path to designing novel anti-viral therapeutics by highlighting the efficacy of DFMO as a broad-spectrum drug, preventing RNA virus replication [244]. Moreover, synthetic spermidine analogues might also serve to prevent microsporidiosis in HIV-infected patients [245]. Also, the FDA-approved anti-viral drug ribavirin, in part, causes polyamine depletion by inducing spermine-spermidine acetyltransferase enzyme activity [246]. The Indole-3-carboxamido-polyamine conjugates also show a broad-spectrum antibacterial activity against *Staphylococcus aureus, Acinetobacter baumannii,* and *Cryptococcus neoformans* (MIC $\leq$0.28 μM) and enhance the doxycycline mediated killing of *Pseudomonas aeruginosa* [247]. Additionally, DFMO treatment in mice infected with typhoid-causing *Salmonella* Typhimurium extended the mice's survival and reduced bacterial burden at the secondary sites of infection [104]. These studies underscore the potential of targeting polyamines in curing infectious disease and pathogenesis.

With the rampant use of antibiotics, we are heading towards a devastating era of antimicrobial resistance, demanding the development of alternative therapeutics to cure the terrifying bacterial diseases. The importance and involvement of polyamines in diverse cellular and molecular roles by most pathogens open avenues to target polyamine metabolism and develop better controlling and curing strategies for infectious diseases. The future requires translating these effective polyamine-targeting drugs and compounds from bench to bedside.

CRediT authorship contribution statement

Abhilash Vijay Nair: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Anmol Singh:** Writing – review & editing, Writing – original draft, Validation, Project administration. **Dipshikha Chakravortty:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The Authors declare no "Conflict of Interest"

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Data availability

No data was used for the research described in the article.

References

[1] L. Rohmer, D. Hocquet, S.I. Miller, Are pathogenic bacteria just looking for food? Metabolism and microbial pathogenesis, Trends Microbiol. 19 (7) (2011) 341–348.
[2] A. Casadevall, L.A. Pirofski, The damage-response framework of microbial pathogenesis, Nat. Rev. Microbiol. 1 (1) (2003) 17–24, https://doi.org/10.1038/nrmicro732.
[3] B.B. Finlay, S. Falkow, Common themes in microbial pathogenicity, Microbiol. Rev. 53 (2) (1989) 210–230, https://doi.org/10.1128/mr.53.2.210-230.1989.
[4] T. Jesudason, WHO publishes updated list of bacterial priority pathogens, Lancet Microbe 5 (9) (2024) 100940, https://doi.org/10.1016/j.lanmic.2024.07.003.
[5] D.V. Parums, Editorial: the World health organization (WHO) fungal priority pathogens list in response to emerging fungal pathogens during the COVID-19 pandemic, Med. Sci. Monit. 28 (2022) e939088, https://doi.org/10.12659/MSM.939088.
[6] G.D. Brown, et al., The pathobiology of human fungal infections, Nat. Rev. Microbiol. 22 (11) (2024) 687–704, https://doi.org/10.1038/s41579-024-01062-w.
[7] E. Lemiech-Mirowska, et al., Nosocomial infections as one of the most important problems of the healthcare system, Ann. Agric. Environ. Med. 28 (3) (2021) 361–366, https://doi.org/10.26444/aaem/122629.
[8] A.S. Monto, et al., Respiratory viral infections from 2015 to 2022 in the HIVE cohort of American households: incidence, illness characteristics, and seasonality, JID (J. Infect. Dis.) 231 (3) (2024) 795–804, https://doi.org/10.1093/infdis/jiae423.
[9] M.A. Lai, et al., Innate immune detection of flagellin positively and negatively regulates salmonella infection, PLoS One 8 (8) (2013) e72047, https://doi.org/10.1371/journal.pone.0072047.
[10] Y. Gu, X.M. Jia, Stealth strategies of Candida albicans to evade host immunity, Cell Host Microbe 32 (9) (2024) 1459–1461, https://doi.org/10.1016/j.chom.2024.08.005.
[11] D. Hajra, A.V. Nair, D. Chakravortty, An elegant nano-injection machinery for sabotaging the host: role of Type III secretion system in virulence of different human and animal pathogenic bacteria, Phys. Life Rev. 38 (2021) 25–54, https://doi.org/10.1016/j.plrev.2021.05.007.
[12] M.A. Blázquez, Polyamines: their role in plant development and stress, Annu. Rev. Plant Biol. 75 (2024), https://doi.org/10.1146/annurev-arplant-070623-110056.
[13] K. Igarashi, K. Kashiwagi, Modulation of cellular function by polyamines, Int. J. Biochem. Cell Biol. 42 (1) (2010) 39–51, https://doi.org/10.1016/j.biocel.2009.07.009.
[14] H.M. Wallace, The polyamines: past, present and future, Essays Biochem. 46 (2009) 1–9, https://doi.org/10.1042/bse0460001.
[15] P. Kalač, Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013, Food Chem. 161 (2014) 27–39, https://doi.org/10.1016/j.foodchem.2014.03.102.
[16] C. Moinard, L. Cynober, J.P. de Bandt, Polyamines: metabolism and implications in human diseases, Clin Nutr 24 (2) (2005) 184–197, https://doi.org/10.1016/j.clnu.2004.11.001.
[17] M. Takigawa, et al., Tumor angiogenesis and polyamines: alpha-difluoromethylornithine, an irreversible inhibitor of ornithine decarboxylase, inhibits B16 melanoma-induced angiogenesis in ovo and the proliferation of vascular endothelial cells in vitro, Cancer Res. 50 (13) (1990) 4131–4138. PMID: 1693880.
[18] C.W. Tabor, H. Tabor, Polyamines in microorganisms, Microbiol. Rev. 49 (1) (1985) 81–99, https://doi.org/10.1128/mr.49.1.81-99.1985.
[19] M.L. Di Martino, et al., Polyamines: emerging players in bacteria–host interactions, International journal of medical microbiology 303 (8) (2013) 484–491, https://doi.org/10.1016/j.ijmm.2013.06.008.
[20] M. Xuan, et al., Polyamines: their significance for maintaining health and contributing to diseases, Cell Commun. Signal. 21 (1) (2023) 348, https://doi.org/10.1186/s12964-023-01373-0.
[21] A. Kaiser, The role of spermidine and its key metabolites in important, pathogenic human viruses and in parasitic infections caused by Plasmodium falciparum and trypanosoma brucei, Biomolecules 13 (5) (2023) 803, https://doi.org/10.3390/biom13050803.
[22] J.B. Goforth, N.E. Walter, E. Karatan, Effects of polyamines on Vibrio cholerae virulence properties, PLoS One 8 (4) (2013) e60765, https://doi.org/10.1371/journal.pone.0060765.
[23] P. Shah, et al., Polyamine biosynthesis and transport mechanisms are crucial for fitness and pathogenesis of Streptococcus pneumoniae, Microbiology (Read.) 157 (Pt 2) (2011) 504–515, https://doi.org/10.1099/mic.0.042564-0.
[24] R. Banerji, P. Kanojiya, S.D. Saroj, Role of interspecies bacterial communication in the virulence of pathogenic bacteria, Crit. Rev. Microbiol. 46 (2) (2020) 136–146, https://doi.org/10.1080/1040841X.2020.1735991.
[25] A.V. Nair, et al., Spermidine constitutes a key determinant of motility and attachment of Salmonella Typhimurium through a novel regulatory mechanism, Microbiol. Res. 281 (2024) 127605, https://doi.org/10.1016/j.micres.2024.127605. ARTN 127605.
[26] T. Miki, et al., Salmonella Typhimurium exploits host polyamines for assembly of the type 3 secretion machinery, PLoS Biol. 22 (8) (2024) e3002731, https://doi.org/10.1371/journal.pbio.3002731.
[27] J. Jiang, et al., Bacterial infection reinforces host metabolic flux from arginine to spermine for NLRP3 inflammasome evasion, Cell Rep. 34 (10) (2021) 108832, https://doi.org/10.1016/j.celrep.2021.108832.
[28] J. Armalytė, et al., A polyamine acetyltransferase regulates the motility and biofilm formation of Acinetobacter baumannii, Nat. Commun. 14 (1) (2023) 3531DOI, https://doi.org/10.1038/s41467-023-39316-5.
[29] S. Sun, V.B. Rao, M.G. Rossmann, Genome packaging in viruses, Curr. Opin. Struct. Biol. 20 (1) (2010) 114–120, https://doi.org/10.1016/j.sbi.2009.12.006.
[30] H.M. Wallace, et al., The effect of polyamines on herpes simplex virus type 1 DNA polymerase purified from infected baby hamster kidney cells (BHK-21/C13),

J. Gen. Virol. 49 (2) (1980) 397–400, https://doi.org/10.1099/0022-1317-49-2-397.
[31] S. Yoshida, S. Masaki, T. Ando, Effects of polyamines on in vitro dna synthesis by DNA polymerases from calf thymus, J. Biochem. 79 (5) (1976) 895–901, https://doi.org/10.1093/oxfordjournals.jbchem.a131157.
[32] W. Gibson, et al., D,L-alpha-difluoromethylornithine inhibits human cytomegalovirus replication, J. Virol. 50 (1) (1984) 145–154, https://doi.org/10.1128/JVI.50.1.145-154.1984.
[33] W. Zhang, H. Chen, J. Zeng, Targeting polyamine metabolism for control of human viral diseases. Infect Drug Resist (2020), https://doi.org/10.2147/IDR.S262024.
[34] S.S. Mahalingam, et al., Polyamine metabolism impacts T cell dysfunction in the oral mucosa of people living with HIV, Nat. Commun. 14 (1) (2023) 399, https://doi.org/10.1038/s41467-023-36163-2.
[35] M.E. Olsen, et al., Polyamines and hypusination are required for Ebolavirus gene expression and replication, mBio 7 (4) (2016), https://doi.org/10.1128/mbio.00882-16, 10.1128/mBio.00882-16.
[36] M.R. Firpo, et al., Targeting polyamines inhibits coronavirus infection by reducing cellular attachment and entry, ACS Infect. Dis. 7 (6) (2021) 1423–1432, https://doi.org/10.1021/acsinfecdis.0c00491.
[37] L.M. Birkholtz, et al., Polyamine homoeostasis as a drug target in pathogenic protozoa: peculiarities and possibilities, Biochem. J. 438 (2) (2011) 229–244, https://doi.org/10.1042/BJ20110362.
[38] S. Roberts, B. Ullman, Parasite polyamines as pharmaceutical targets, Curr. Pharm. Des. 23 (23) (2017) 3325–3341, https://doi.org/10.2174/1381612823666170601101644.
[39] M.C. Vanrell, et al., Polyamine depletion inhibits the autophagic response modulating Trypanosoma cruzi infectivity, Autophagy 9 (7) (2013) 1080–1093, https://doi.org/10.4161/auto.24709.
[40] N. LoGiudice, et al., Alpha-difluoromethylornithine, an irreversible inhibitor of polyamine biosynthesis, as a therapeutic strategy against hyperproliferative and infectious diseases, Medical Sciences 6 (1) (2018) 12, https://doi.org/10.3390/medsci6010012.
[41] C. Reigada, et al., Trypanosoma cruzi polyamine transporter: its role on parasite growth and survival under stress conditions, J. Membr. Biol. 249 (4) (2016) 475–481, https://doi.org/10.1007/s00232-016-9888-z.
[42] M.V. Díaz, et al., Pentamidine exerts in vitro and in vivo anti Trypanosoma cruzi activity and inhibits the polyamine transport in Trypanosoma cruzi, Acta Trop. 134 (2014) 1–9, https://doi.org/10.1016/j.actatropica.2014.02.012.
[43] J.M. Boitz, et al., Leishmania donovani ornithine decarboxylase is indispensable for parasite survival in the mammalian host, Infect. Immun. 77 (2) (2009) 756–763, https://doi.org/10.1128/IAI.01236-08.
[44] S. Hatmi, et al., Osmotic stress-induced polyamine oxidation mediates defence responses and reduces stress-enhanced grapevine susceptibility to Botrytis cinerea, J. Exp. Bot. 65 (1) (2014) 75–88, https://doi.org/10.1093/jxb/ert351.
[45] C. Liu, et al., The polyamine putrescine contributes to H(2)O(2) and RbohD/F-dependent positive feedback loop in Arabidopsis PAMP-triggered immunity, Front. Plant Sci. 10 (2019) 894, https://doi.org/10.3389/fpls.2019.00894.
[46] J.M. Vilas, et al., Modulation of plant and bacterial polyamine metabolism during the compatible interaction between tomato and, J. Plant Physiol. 231 (2018) 281–290, https://doi.org/10.1016/j.jplph.2018.09.014.
[47] D. Wu, et al., A plant pathogen type III effector protein subverts translational regulation to boost host polyamine levels, Cell Host Microbe 26 (5) (2019) 638–649, https://doi.org/10.1016/j.chom.2019.09.014, e5.
[48] D.M. Monack, A. Mueller, S. Falkow, Persistent bacterial infections: the interface of the pathogen and the host immune system, Nat. Rev. Microbiol. 2 (9) (2004) 747–765, https://doi.org/10.1038/nrmicro955.
[49] J.E. Gomez, J.D. McKinney, M. tuberculosis persistence, latency, and drug tolerance, Tuberculosis 84 (1–2) (2004) 29–44, https://doi.org/10.1016/j.tube.2003.08.003.
[50] D. Liu, et al., Innate immune effectors play essential roles in acute respiratory infection caused by Klebsiella pneumoniae, J Immunol Res 2020 (1) (2020) 5291714, https://doi.org/10.1155/2020/5291714.
[51] A. Iwasaki, P.S. Pillai, Innate immunity to influenza virus infection, Nat. Rev. Immunol. 14 (5) (2014) 315–328, https://doi.org/10.1038/nri3665.
[52] L. Cavinato, et al., Escaping the phagocytic oxidative burst: the role of SODB in the survival of within macrophages, Front. Microbiol. 11 (2020) 326. ARTN.32610.3389/fmicb.2020.00326.
[53] D. Camejo, Á. Guzmán-Cedeño, A. Moreno, Reactive oxygen species, essential molecules, during plant–pathogen interactions, Plant Physiol. Biochem. 103 (2016) 10–23, https://doi.org/10.1016/j.plaphy.2016.02.035.
[54] M.B. Hampton, N. Dickerhof, Inside the phagosome: a bacterial perspective, Immunol. Rev. 314 (1) (2023) 197–209, https://doi.org/10.1111/imr.13182.
[55] J.M. Slauch, How does the oxidative burst of macrophages kill bacteria? Still an open question, Mol. Microbiol. 80 (3) (2011) 580–583, https://doi.org/10.1111/j.1365-2958.2011.07612.x.
[56] M. Fasnacht, N. Polacek, Oxidative stress in bacteria and the central dogma of molecular biology, Front. Mol. Biosci. 8 (2021) 671037, https://doi.org/10.3389/fmolb.2021.671037.
[57] H. Sies, Hydroperoxides and thiol oxidants in the study of oxidative stress in intact cells and organs, Oxidative stress 1 (1985) 73–90, https://doi.org/10.1016/B978-0-12-642760-8.50008-9.
[58] H. Sies, Oxidative stress: a concept in redox biology and medicine, Redox Biol. 4 (2015) 180–183, https://doi.org/10.1016/j.redox.2015.01.002.
[59] H. Sies, Biochemistry of oxidative stress, Angewandte Chemie-International Edition 25 (12) (1986) 1058–1071, https://doi.org/10.1002/anie.198610581.
[60] C.A. Juan, et al., The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies, Int. J. Mol. Sci. 22 (9) (2021) 4642, https://doi.org/10.3390/ijms22094642. ARTN 4642.
[61] K.O. Muranov, Fenton reaction in vivo and in vitro. Possibilities and limitations, Biochemistry (Mosc) 89 (Suppl 1) (2024) S112–S126, https://doi.org/10.1134/S0006297924140074.
[62] C. Prolo, M.N. Alvarez, R. Radi, Peroxynitrite, a potent macrophage-derived oxidizing cytotoxin to combat invading pathogens, Biofactors 40 (2) (2014) 215–225, https://doi.org/10.1002/biof.1150.
[63] R.D. Novaes, A.L. Teixeira, A.S. de Miranda, Oxidative stress in microbial diseases: pathogen, host, and therapeutics, Oxid. Med. Cell. Longev. 2019 (2019) 8159562, https://doi.org/10.1155/2019/8159562.
[64] F.C. Fang, et al., Bacterial stress responses during host infection, Cell Host Microbe 20 (2) (2016) 133–143, https://doi.org/10.1016/j.chom.2016.07.009.
[65] M.A. Kohanski, et al., A common mechanism of cellular death induced by bactericidal antibiotics, Cell 130 (5) (2007) 797–810, https://doi.org/10.1016/j.cell.2007.06.049.
[66] M. de Souza Santos, D. Salomon, K. Orth, T3SS effector VopL inhibits the host ROS response, promoting the intracellular survival of Vibrio parahaemolyticus, PLoS Pathog. 13 (6) (2017) e1006438, https://doi.org/10.1371/journal.ppat.1006438.
[67] A.T. Dharmaraja, Role of reactive oxygen species (ROS) in therapeutics and drug resistance in cancer and bacteria, J. Med. Chem. 60 (8) (2017) 3221–3240, https://doi.org/10.1021/acs.jmedchem.6b01243.
[68] A. Martner, et al., Pneumolysin released during autolysis is a potent activator of intracellular oxygen radical production in neutrophils, Infect. Immun. 76 (9) (2008) 4079–4087, https://doi.org/10.1128/Iai.01747-07.
[69] R.L. Krauth-Siegel, M.A. Comini, Redox control in trypanosomatids, parasitic protozoa with trypanothione-based thiol metabolism, Biochim. Biophys. Acta 1780 (11) (2008) 1236–1248, https://doi.org/10.1016/j.bbagen.2008.03.006.
[70] B. Manta, et al., Trypanothione: a unique bis-glutathionyl derivative in trypanosomatids, Biochim. Biophys. Acta 1830 (5) (2013) 3199–3216, https://doi.org/10.1016/j.bbagen.2013.01.013.
[71] B.Y. Chiang, et al., Protein S-thiolation by Glutathionylspermidine (Gsp): the role of Escherichia coli Gsp synthetASE/amidase in redox regulation, J. Biol. Chem. 285 (33) (2010) 25345–25353, https://doi.org/10.1074/jbc.M110.133363.
[72] D.E. Larcombe, et al., Glucose-enhanced oxidative stress resistance—a protective anticipatory response that enhances the fitness of Candida albicans during systemic infection, PLoS Pathog. 19 (7) (2023) e1011505, https://doi.org/10.1371/journal.ppat.1011505.
[73] L.D. Butcher, et al., Oxidative stress resulting from Helicobacter pylori infection contributes to gastric carcinogenesis, Cell. Mol. Gastroenterol. Hepatol. 3 (3) (2017) 316–322, https://doi.org/10.1016/j.jcmgh.2017.02.002.
[74] H. Yang, et al., Chlamydia psittaci infection induces IFN-I and IL-1β through the cGAS-STING-IRF3/NLRP3 pathway via mitochondrial oxidative stress in human macrophages, Vet. Microbiol. 299 (2024) 110292, https://doi.org/10.1016/j.vetmic.2024.110292.
[75] O.K. Kumova, et al., Severity of neonatal influenza infection is driven by type I interferon and oxidative stress, Mucosal Immunol. 15 (6) (2022) 1309–1320, https://doi.org/10.1038/s41385-022-00576-x.
[76] C. Piccoli, et al., Hepatitis C virus protein expression causes calcium-mediated mitochondrial bioenergetic dysfunction and nitro-oxidative stress, Hepatology 46 (1) (2007) 58–65, https://doi.org/10.1002/hep.21679.
[77] D. Yamane, et al., Regulation of the hepatitis C virus RNA replicase by endogenous lipid peroxidation, Nat Med 20 (8) (2014) 927–935, https://doi.org/10.1038/nm.3610.
[78] S. Anticoli, et al., Erratum to “counteraction of HCV-induced oxidative stress concurs to establish chronic infection in liver cell cultures”, Oxid. Med. Cell. Longev. 2019 (2019) https://doi.org/10.1155/2019/6452390.
[79] K. Machida, et al., Hepatitis C virus infection activates the immunologic (type II) isoform of nitric oxide synthase and thereby enhances DNA damage and mutations of cellular genes, J. Virol. 78 (16) (2004) 8835–8843, https://doi.org/10.1128/JVI.78.16.8835-8843.2004.
[80] K. Machida, et al., Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation, J. Virol. 80 (14) (2006) 7199–7207, https://doi.org/10.1128/JVI.00321-06.
[81] Y. Tian, et al., Inhibitory effects of glutathione on dengue virus production, Biochem. Biophys. Res. Commun. 397 (3) (2010) 420–424, https://doi.org/10.1016/j.bbrc.2010.05.108.
[82] A.C. Ferraz, et al., Yellow fever virus infection in human hepatocyte cells triggers an imbalance in redox homeostasis with increased reactive oxygen species production, oxidative stress, and decreased antioxidant enzymes, Free Radic. Biol. Med. 213 (2024) 266–273, https://doi.org/10.1016/j.freeradbiomed.2024.01.042.
[83] Y. Htet, et al., Hydrogen peroxide as a hydride donor and reductant under biologically relevant conditions, Chem. Sci. 10 (7) (2019) 2025–2033, https://doi.org/10.1039/c8sc05418e.
[84] H. Sies, Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: oxidative eustress, Redox Biol. 11 (2017) 613–619, https://doi.org/10.1016/j.redox.2016.12.035.
[85] L.C.P. Dharshini, et al., Oxidative stress responsive transcription factors in cellular signalling transduction mechanisms, Cell. Signal. 72 (2020) 109670, https://doi.org/10.1016/j.cellsig.2020.109670. ARTN 109670.

[86] D.A. Averill-Bates, The antioxidant glutathione, in: Vitamins and Hormones, Elsevier, 2023, pp. 109–141, https://doi.org/10.1016/bs.vh.2022.09.002.

[87] F. Nazir, Q. Fariduddin, T.A. Khan, Hydrogen peroxide as a signalling molecule in plants and its crosstalk with other plant growth regulators under heavy metal stress, Chemosphere 252 (2020) 126486, https://doi.org/10.1016/j.chemosphere.2020.126486. ARTN 12648.

[88] T.M. Stewart, et al., Polyamine catabolism and oxidative damage, J. Biol. Chem. 293 (48) (2018) 18736–18745, https://doi.org/10.1074/jbc.TM118.003337.

[89] W. Wang, et al., Polyamine catabolism in plants: a universal process with diverse functions, Front. Plant Sci. 10 (2019) 561, https://doi.org/10.3389/fpls.2019.00561.

[90] P.N. Moschou, et al., Engineered polyamine catabolism preinduces tolerance of tobacco to bacteria and oomycetes, Plant Physiol 149 (4) (2009) 1970–1981, https://doi.org/10.1104/pp.108.134932.

[91] I. Pottosin, et al., Cross-talk between reactive oxygen species and polyamines in regulation of ion transport across the plasma membrane: implications for plant adaptive responses, J. Exp. Bot. 65 (5) (2014) 1271–1283, https://doi.org/10.1093/jxb/ert423.

[92] Y. Li, et al., Exogenous polyamines enhance resistance to Alternaria alternata by modulating redox homeostasis in apricot fruit, Food Chem. 301 (2019) 125303, https://doi.org/10.1016/j.foodchem.2019.125303.

[93] A.P. Gobert, K.T. Wilson, Polyamine- and NADPH-dependent generation of ROS during Helicobacter pylori infection: a blessing in disguise, Free Radic. Biol. Med. 105 (2017) 16–27, https://doi.org/10.1016/j.freeradbiomed.2016.09.024.

[94] O.A. Smirnova, et al., Polyamine metabolism and oxidative protein folding in the ER as ROS-producing systems neglected in virology, Int. J. Mol. Sci. 19 (4) (2018) 1219, https://doi.org/10.3390/ijms19041219. ARTN 1219.

[95] K.C. Das, H.P. Misra, Hydroxyl radical scavenging and singlet oxygen quenching properties of polyamines, Mol. Cell. Biochem. 262 (1–2) (2004) 127–133, https://doi.org/10.1023/b:mcbi.0000038227.91813.79.

[96] H.C. Ha, et al., The natural polyamine spermine functions directly as a free radical scavenger, Proceedings of the National Academy of Sciences of the United States of America 95 (19) (1998) 11140–11145, https://doi.org/10.1073/pnas.95.19.11140.

[97] I.L. Jung, I.G. Kim, Transcription of and genes in is regulated by polyamines:: polyamine-deficient mutant sensitive to HO-induced oxidative damage, Biochem. Biophys. Res. Commun. 301 (4) (2003) 915–922, https://doi.org/10.1016/S0006-291x(03)00064-0.

[98] A.J. Michael, Polyamine function in archaea and bacteria, J. Biol. Chem. 293 (48) (2018) 18693–18701, https://doi.org/10.1074/jbc.TM118.005670.

[99] R. Banerji, et al., Polyamines in the virulence of bacterial pathogens of respiratory tract, Mol Oral Microbiol 36 (1) (2021) 1–11, https://doi.org/10.1111/omi.12315.

[100] Y.Y. Lenis, et al., Physiological importance of polyamines, Zygote 25 (3) (2017) 244–255, https://doi.org/10.1017/S0967199417000120.

[101] J.M. Durand, G.R. Bjork, Putrescine or a combination of methionine and arginine restores virulence gene expression in a tRNA modification-deficient mutant of Shigella flexneri: a possible role in adaptation of virulence, Mol. Microbiol. 47 (2) (2003) 519–527, https://doi.org/10.1046/j.1365-2958.2003.03314.x.

[102] M. Barbagallo, et al., A new piece of the pathogenicity puzzle: spermidine accumulationby silencing of the gene, PLoS One 6 (11) (2011) e27226. ARTN. e2722610.1371/journal.pone.0027226.

[103] H.C. Ha, et al., The natural polyamine spermine functions directly as a free radical scavenger, Proc. Natl. Acad. Sci. U. S. A. 95 (19) (1998) 11140–11145, https://doi.org/10.1073/pnas.95.19.11140.

[104] A.V. Nair, et al., Salmonella Typhimurium employs spermidine to exert protection against ROS-mediated cytotoxicity and rewires host polyamine metabolism to ameliorate its survival in macrophages, Redox Biol. 72 (2024) 103151, https://doi.org/10.1016/j.redox.2024.103151.

[105] A.G. Tkachenko, L.Y. Nesterova, Polyamines as modulators of gene expression under oxidative stress in, Biochemistry-Moscow 68 (8) (2003) 850–856, https://doi.org/10.1023/A:1025790729797.

[106] Y. Terui, et al., Enhancement of the synthesis of RpoN, Cra, and H-NS by polyamines at the level of translation in cultured with glucose and glutamate, J. Bacteriol. 189 (6) (2007) 2359–2368, https://doi.org/10.1128/Jb.01562-06.

[107] J.M. Bower, M.A. Mulvey, Polyamine-mediated resistance of uropathogenic Escherichia coli to nitrosative stress, J. Bacteriol. 188 (3) (2006) 928–933, https://doi.org/10.1128/JB.188.3.928-933.2006.

[108] R. Banerji, P. Iyer, S.D. Saroj, Spermidine enhances the survival of Streptococcus pyogenes M3 under oxidative stress, Mol Oral Microbiol 37 (2) (2022) 53–62, https://doi.org/10.1111/omi.12360.

[109] M.F. Nakamya, et al., Polyamine transport is required for stress responses and capsule production in Streptococcus pneumoniae, Pathogens 10 (10) (2021), https://doi.org/10.21203/rs.3.rs-192362/v1.

[110] A.G. Tkachenko, et al., Polyamines reduce oxidative stress in Escherichia coli cells exposed to bactericidal antibiotics, Res. Microbiol. 163 (2) (2012) 83–91, https://doi.org/10.1016/j.resmic.2011.10.009.

[111] L. Johnson, et al., Surface-localized spermidine protects the Pseudomonas aeruginosa outer membrane from antibiotic treatment and oxidative stress, J. Bacteriol. 194 (4) (2012) 813–826, https://doi.org/10.1128/JB.05230-11.

[112] S. Tiwari, et al., Arginine-deprivation–induced oxidative damage sterilizes Mycobacterium tuberculosis, Proc. Natl. Acad. Sci. 115 (39) (2018) 9779–9784, https://doi.org/10.1073/pnas.180887411.

[113] C. Sao Emani, N. Reiling, Spermine enhances the activity of anti-tuberculosis drugs, Microbiol. Spectr. 12 (1) (2024) e0356823, https://doi.org/10.1128/spectrum.03568-23.

[114] R. Chaturvedi, et al., Increased pylori-associated gastric cancer risk in the Andean region of Colombia is mediated by spermine oxidase, Oncogene 34 (26) (2015) 3429–3440, https://doi.org/10.1038/onc.2014.273.

[115] J.C. Sierra, et al., Spermine oxidase mediates Helicobacter pylori-induced gastric inflammation, DNA damage, and carcinogenic signaling, Oncogene 39 (22) (2020) 4465–4474, https://doi.org/10.1038/s41388-020-1304-6.

[116] T. Murray-Stewart, et al., Epigenetic silencing of miR-124 prevents spermine oxidase regulation: implications for Helicobacter pylori-induced gastric cancer, Oncogene 35 (42) (2016) 5480–5488, https://doi.org/10.1038/onc.2016.91.

[117] A.C. Goodwin, et al., Polyamine catabolism contributes to enterotoxigenic Bacteroides fragilis-induced colon tumorigenesis, Proc. Natl. Acad. Sci. U. S. A. 108 (37) (2011) 15354–15359, https://doi.org/10.1073/pnas.1010203108.

[118] R.V. Purcell, et al., Colonization with enterotoxigenic is associated with early-stage colorectal neoplasia, PLoS One 12 (2) (2017) e0171602, https://doi.org/10.1371/journal.pone.0171602. ARTN e0171602.

[119] C. Xie, et al., Polyamine signaling communications play a key role in regulating the pathogenicity of Dickeya fangzhongdai, Microbiol. Spectr. 11 (6) (2023) e0196523, https://doi.org/10.1128/spectrum.01965-23.

[120] Z. Shi, et al., Putrescine is an intraspecies and interkingdom cell-cell communication signal modulating the virulence of Dickeya zeae, Front. Microbiol. 10 (2019) 1950, https://doi.org/10.3389/fmicb.2019.01950.

[121] L. Solmi, et al., Polyamine-mediated mechanisms contribute to oxidative stress tolerance in Pseudomonas syringae, Sci. Rep. 13 (1) (2023) 4279, https://doi.org/10.1038/s41598-023-31239-x.

[122] C. Liu, et al., Putrescine elicits ROS-dependent activation of the salicylic acid pathway in Arabidopsis thaliana, Plant Cell Environ. 43 (11) (2020) 2755–2768, https://doi.org/10.1111/pce.13874.

[123] A.I. Chavez-Martinez, et al., Arabidopsis adc-silenced line exhibits differential defense responses to Botrytis cinerea and Pseudomonas syringae infection, Plant Physiol Biochem 156 (2020) 494–503, https://doi.org/10.1016/j.plaphy.2020.09.035.

[124] M. Marina, et al., Apoplastic polyamine oxidation plays different roles in local responses of tobacco to infection by the necrotrophic fungus Sclerotinia sclerotiorum and the biotrophic bacterium Pseudomonas viridiflava, Plant Physiol 147 (4) (2008) 2164–2178, https://doi.org/10.1104/pp.108.122614.

[125] H. Yoda, et al., Polyamines as a common source of hydrogen peroxide in host- and nonhost hypersensitive response during pathogen infection, Plant Mol. Biol. 70 (1–2) (2009) 103–112, https://doi.org/10.1007/s11103-009-9459-0.

[126] J. Hidalgo-Castellanos, et al., Polyamines oxidation is required in the symbiotic interaction Medicago truncatula–Sinorhizobium meliloti but does not participate in the regulation of polyamines level under salinity, Plant Growth Regul. 88 (2019) 297–307, https://doi.org/10.1007/s10725-019-00508-z.

[127] L. Gerlin, C. Baroukh, S. Genin, Polyamines: double agents in disease and plant immunity, Trends Plant Sci. 26 (10) (2021) 1061–1071, https://doi.org/10.1016/j.tplants.2021.05.007.

[128] S. Yina, et al., The first description of complete invertebrate arginine metabolism pathways implies dose-dependent pathogen regulation in Apostichopus japonicus, Sci. Rep. 6 (1) (2016) 23783, https://doi.org/10.1038/srep23783.

[129] T. Hinzke, et al., Host-microbe interactions in the chemosynthetic Riftia pachyptila symbiosis, mBio 10 (6) (2019), https://doi.org/10.1128/mbio.02243-19, 10.1128/mBio.02243-19.

[130] B. Brissette, et al., Chemosensory detection of polyamine metabolites guides C. elegans to nutritive microbes, Sci. Adv. 10 (12) (2024) eadj4387, https://doi.org/10.1126/sciadv.adj4387.

[131] S.C. Riemer, V.A. Bloomfield, Packaging of DNA in bacteriophage heads: some considerations on energetics, Biopolymers: Original Research on Biomolecules 17 (3) (1978) 785–794, https://doi.org/10.1002/bip.1978.360170317.

[132] D.V. Young, P. Srinivasan, Growth of ribonucleic acid bacteriophage f2 in a conditional putrescine auxotroph of Escherichia coli: evidence for a polyamine role in translation, J. Bacteriol. 117 (3) (1974) 1280–1288, https://doi.org/10.1128/jb.117.3.1280-1288.1974, 10.1073/pnas.68.11.2818.

[133] W. Gibson, B. Roizman, Compartmentalization of spermine and spermidine in the herpes simplex virion, Proc. Natl. Acad. Sci. 68 (11) (1971), 2818-282.

[134] A. Tyms, J. Williamson, Inhibitors of polyamine biosynthesis block human cytomegalovirus replication, Nature 297 (5868) (1982) 690–691, https://doi.org/10.1073/pnas.68.11.2818.

[135] A.V. Ivanov, et al., HCV core protein uses multiple mechanisms to induce oxidative stress in human hepatoma Huh7 cells, Viruses 7 (6) (2015) 2745–2770, https://doi.org/10.3390/v7062745.

[136] O.A. Smirnova, et al., Hepatitis C virus NS5A protein triggers oxidative stress by inducing NADPH oxidases 1 and 4 and cytochrome P450 2E1, Oxid. Med. Cell. Longev. 2016 (1) (2016) 8341937.

[137] O.A. Smirnova, et al., Hepatitis C virus alters metabolism of biogenic polyamines by affecting expression of key enzymes of their metabolism, Biochem. Biophys. Res. Commun. 483 (2) (2017) 904–909, https://doi.org/10.1155/2016/8341937.

[138] F. Chen, et al., Citraconate inhibits ACOD1 (IRG1) catalysis, reduces interferon responses and oxidative stress, and modulates inflammation and cell metabolism, Nat. Metab. 4 (5) (2022) 534–546, https://doi.org/10.1038/s42255-022-00577-x.

[139] H. Xie, et al., PEDV infection affects the expression of polyamine-related genes inhibiting viral proliferation, Virus Res. 312 (2022) 198708.

[140] C. Capone, et al., A role for spermine oxidase as a mediator of reactive oxygen species production in HIV-Tat-induced neuronal toxicity, Free Radic. Biol. Med. 63 (2013) 99–107, https://doi.org/10.1016/j.freeradbiomed.2013.05.007.

[141] S.J. Klebanoff, F. Kazazi, Inactivation of human immunodeficiency virus type 1 by the amine oxidase-peroxidase system, J. Clin. Microbiol. 33 (8) (1995) 2054–2057, https://doi.org/10.1128/jcm.33.8.2054-2057.1995.
[142] B.C. Mounce, et al., Interferon-induced spermidine-spermine acetyltransferase and polyamine depletion restrict zika and Chikungunya viruses, Cell Host Microbe 20 (2) (2016) 167–177, https://doi.org/10.1016/j.chom.2016.06.011.
[143] T.M. Kicmal, et al., Polyamine depletion abrogates enterovirus cellular attachment, J. Virol. 93 (20) (2019), https://doi.org/10.1128/jvi.01054-19, 10.1128/JVI.01054-19.
[144] C.N. Dial, et al., Coxsackievirus B3 responds to polyamine depletion via enhancement of 2A and 3C protease activity, Viruses 11 (5) (2019) 403, https://doi.org/10.3390/v11050403.
[145] V. Sekar, et al., Inhibition of ornithine decarboxylase in human fibroblast cells by type I and type II interferons, Biochem. Biophys. Res. Commun. 114 (3) (1983) 950–954, https://doi.org/10.1016/0006-291x(83)90652-6.
[146] S.H. Spoel, X. Dong, How do plants achieve immunity? Defence without specialized immune cells, Nat. Rev. Immunol. 12 (2) (2012) 89–100, https://doi.org/10.1038/nri3141.
[147] A. Levine, et al., H2O2 from the oxidative burst orchestrates the plant hypersensitive disease resistance response, Cell 79 (4) (1994) 583–593, https://doi.org/10.1016/0092-8674(94)90544-4.
[148] J. Wu, et al., ROS accumulation and antiviral defence control by microRNA528 in rice, Nat. Plants 3 (1) (2017) 1–7, https://doi.org/10.1038/nplants.2016.203.
[149] X. Liu, et al., Maize miR167-ARF3/30-polyamine oxidase 1 module-regulated H2O2 production confers resistance to maize chlorotic mottle virus, Plant Physiol 189 (2) (2022) 1065–1082, https://doi.org/10.1093/plphys/kiac099.
[150] J.A. Hernández, et al., Oxidative stress and antioxidative responses in plant–virus interactions, Physiol. Mol. Plant Pathol. 94 (2016) 134–148, https://doi.org/10.1016/j.pmpp.2015.09.001.
[151] J. Yang, et al., TaTHI2 interacts with Ca2+-dependent protein kinase TaCPK5 to suppress virus infection by regulating ROS accumulation, Plant Biotechnol. J. 22 (5) (2024) 1335–1351, https://doi.org/10.1111/pbi.14270.
[152] A. Nagai, et al., Signaling pathway played by salicylic acid, gentisic acid, nitric oxide, polyamines and non-enzymatic antioxidants in compatible and incompatible Solanum-tomato mottle mosaic virus interactions, Plant Sci. 290 (2020) 110274, https://doi.org/10.1016/j.plantsci.2019.110274.
[153] Y. Mitsuya, et al., Spermine signaling plays a significant role in the defense response of Arabidopsis thaliana to cucumber mosaic virus, J. Plant Physiol. 166 (6) (2009) 626–643, https://doi.org/10.1016/j.jplph.2008.08.006.
[154] G.H.M. Sagor, et al., Exogenous thermospermine has an activity to induce a subset of the defense genes and restrict cucumber mosaic virus multiplication in, Plant Cell Rep. 31 (7) (2012) 1227–1232, https://doi.org/10.1007/s00299-012-1243-y.
[155] Y.J. Liu, H.J. Zhang, Reactive oxygen species and nitric oxide as mediators in plant hypersensitive response and stomatal closure, Plant Signal. Behav. 16 (12) (2021) 1985860, https://doi.org/10.1080/15592324.2021.1985860.
[156] H. Yoda, Y. Yamaguchi, H. Sano, Induction of hypersensitive cell death by hydrogen peroxide produced through polyamine degradation in tobacco plants, Plant Physiology 132 (4) (2003) 1973–1981, https://doi.org/10.1104/pp.103.024737.
[157] L. Kiraly, et al., Reactive oxygen species contribute to symptomless, extreme resistance to Potato virus X in tobacco, Phytopathology 111 (10) (2021) 1870–1884, https://doi.org/10.1094/PHYTO-12-20-0540-R.
[158] Y.D. Sun, S.Y. Folimonova, The p33 protein of Citrus tristeza virus affects viral pathogenicity by modulating a host immune response, New Phytol. 221 (4) (2019) 2039–2053, https://doi.org/10.1111/nph.15482.
[159] H. Chen, et al., Identification of differentially regulated maize proteins conditioning Sugarcane mosaic virus systemic infection, New Phytol. 215 (3) (2017) 1156–1172, https://doi.org/10.1111/nph.14645.
[160] F.F. Norman, et al., Update on the major imported protozoan infections in travelers and migrants, Future Microbiol. 15 (3) (2020) 213–225, https://doi.org/10.2217/fmb-2019-0212.
[161] R. Stephens, J.E. Uzonna, S.M. Dann, Host defenses to Protozoa, in: Clinical Immunology: Principles and Practice, sixth ed., Elsevier, 2022, pp. 375–385, https://doi.org/10.1016/B978-0-7020-8165-1.00029-0.
[162] A.H. Fairlamb, Trypanothione metabolism and rational approaches to drug design, Biochem. Soc. Trans. 18 (5) (1990) 717–720, https://doi.org/10.1042/bst0180717.
[163] A.H. Fairlamb, et al., Trypanothione: a novel bis(glutathionyl)spermidine cofactor for glutathione reductase in trypanosomatids, Science 227 (4693) (1985) 1485–1487, https://doi.org/10.1126/science.3883489.
[164] E. Maldonado, et al., Dual and opposite roles of reactive oxygen species (ROS) in Chagas disease: beneficial on the pathogen and harmful on the host, Oxid. Med. Cell. Longev. 2020 (1) (2020) 8867701, https://doi.org/10.1155/2020/8867701.
[165] K.B. Dickson, J. Zhou, Role of reactive oxygen species and iron in host defense against infection, Front. Biosci. (Landmark Ed.) 25 (8) (2020) 1600–1616, https://doi.org/10.2741/4869.
[166] G. Sorci, B. Faivre, Inflammation and oxidative stress in vertebrate host–parasite systems, Phil. Trans. Biol. Sci. 364 (1513) (2009) 71–83, https://doi.org/10.1098/rstb.2008.0151.
[167] M. Lopez, H.B. Tanowitz, N.J. Garg, Pathogenesis of chronic Chagas disease: macrophages, mitochondria, and oxidative stress, Curr. Clin. Microbiol. Rep. 5 (1) (2018) 45–54, https://doi.org/10.1007/s40588-018-0081-2.
[168] A.C. Mesías, et al., Trypanothione synthetase confers growth, survival advantage and resistance to anti-protozoal drugs in Trypanosoma cruzi, Free Radic. Biol. Med. 130 (2019) 23–34, https://doi.org/10.1016/j.freeradbiomed.2018.10.436.
[169] M. Akhoundi, et al., A historical overview of the classification, evolution, and dispersion of Leishmania parasites and sandflies, PLoS Negl Trop Dis 10 (3) (2016) e0004349, https://doi.org/10.1371/journal.pntd.0004349.
[170] A.D. Kennedy, F.R. DeLeo, Neutrophil apoptosis and the resolution of infection, Immunol. Res. 43 (1–3) (2009) 25–61, https://doi.org/10.1007/s12026-008-8049-6.
[171] A.B. Guimaraes-Costa, et al., 3'-nucleotidase/nuclease activity allows Leishmania parasites to escape killing by neutrophil extracellular traps, Infect. Immun. 82 (4) (2014) 1732–1740, https://doi.org/10.1128/IAI.01232-13.
[172] A.B. Guimaraes-Costa, et al., Neutrophil extracellular traps reprogram IL-4/GM-CSF-induced monocyte differentiation to anti-inflammatory macrophages, Front. Immunol. 8 (2017) 523, https://doi.org/10.3389/fimmu.2017.00523.
[173] F. Aktan, iNOS-mediated nitric oxide production and its regulation, Life Sci. 75 (6) (2004) 639–653, https://doi.org/10.1016/j.lfs.2003.10.042.
[174] A. Panday, et al., NADPH oxidases: an overview from structure to innate immunity-associated pathologies, Cell. Mol. Immunol. 12 (1) (2015) 5–23, https://doi.org/10.1038/cmi.2014.89.
[175] M.B.H. Carneiro, et al., NOX2-Derived reactive oxygen species control inflammation during Leishmania amazonensis infection by mediating infection-induced neutrophil apoptosis, J. Immunol. 200 (1) (2018) 196–208, https://doi.org/10.4049/jimmunol.1700899.
[176] N.K. Pham, J. Mouriz, P.E. Kima, Leishmania pifanoi amastigotes avoid macrophage production of superoxide by inducing heme degradation, Infect. Immun. 73 (12) (2005) 8322–8333, https://doi.org/10.1128/IAI.73.12.8322-8333.2005.
[177] H. Malta-Santos, et al., Differential expression of polyamine biosynthetic pathways in skin lesions and in plasma reveals distinct profiles in diffuse cutaneous leishmaniasis, Sci. Rep. 10 (1) (2020) 10543, https://doi.org/10.1038/s41598-020-67432-5.
[178] N. Velez, M.A. Phillips, Targeting the polyamine biosynthetic pathway in parasitic protozoa, Polyamines: A Universal Molecular Nexus for Growth, Survival, and Specialized Metabolism (2015) 315–329, https://doi.org/10.1007/978-4-431-55212-3_24.
[179] S. Singh, et al., Probing the molecular mechanism of hypericin-induced parasite death provides insight into the role of spermidine beyond redox metabolism in, Antimicrob. Agents Chemother. 59 (1) (2015) 15–24, https://doi.org/10.1128/Aac.04169-14.
[180] A. Yadav, et al., Impairment of the cellular immune response against recombinant ornithine decarboxylase protein as a possible evasion strategy of in visceral leishmaniasis, Int. J. Parasitol. 45 (1) (2015) 33–42, https://doi.org/10.1016/j.ijpara.2014.08.013.
[181] P. Sebastian, et al., Polyamine-enriched exosomes from Leishmania donovani drive host macrophage polarization via immunometabolism reprogramming, ACS Infect. Dis. 10 (12) (2024) 4384–4399, https://doi.org/10.1021/acsinfecdis.4c00738.
[182] J.C.R. Fernandes, et al., Early Leishmania infectivity depends on miR-372/373/520d family-mediated reprogramming of polyamines metabolism in THP-1-derived macrophages, Sci. Rep. 14 (1) (2024) 996, https://doi.org/10.1038/s41598-024-51511-y.
[183] A.K. Ghosh, et al., Metabolic reconfiguration of the central glucose metabolism: a crucial strategy of Leishmania donovani for its survival during oxidative stress, FASEB J. 29 (5) (2015) 2081–2098, https://doi.org/10.1096/fj.14-258624.
[184] M. Kamil, et al., Mitochondrial spermidine synthase is essential for blood-stage growth of the malaria parasite, Microbiol. Res. 265 (2022) 127181. ARTN.12718110.1016/j.micres.2022.127181.
[185] P. Singh, C.B. Mamoun, Spermidine is the main polyamine required by intracellular parasites for survival within host erythrocytes, bioRxiv (2023) 2023, https://doi.org/10.1101/2023.02.01.526700, 02. 01.526700.
[186] C.M. Rzepczyk, A.J. Saul, A. Ferrante, Polyamine oxidase-mediated intraerythrocytic killing of Plasmodium falciparum: evidence against the role of reactive oxygen metabolites, Infect. Immun. 43 (1) (1984) 238–244, https://doi.org/10.1128/iai.43.1.238-244.1984.
[187] T.M. Nelson, et al., Vaginal biogenic amines: biomarkers of bacterial vaginosis or precursors to vaginal dysbiosis? Front. Physiol. 6 (2015) 253, https://doi.org/10.3389/fphys.2015.00253.
[188] M.E. Alvarez-Sanchez, et al., Proteomic profile approach of effect of putrescine depletion over Trichomonas vaginalis, Parasitol. Res. 117 (5) (2018) 1371–1380, https://doi.org/10.1007/s00436-018-5821-y.
[189] J.R. Schwebke, F.J. Barrientes, Prevalence of Trichomonas vaginalis isolates with resistance to metronidazole and tinidazole, Antimicrob. Agents Chemother. 50 (12) (2006) 4209–4210, https://doi.org/10.1128/AAC.00814-06.
[190] S.N. Moreno, R. Docampo, Mechanism of toxicity of nitro compounds used in the chemotherapy of trichomoniasis, Environ. Health Perspect. 64 (1985) 199–208, https://doi.org/10.1289/ehp.8564199.
[191] G.V. Rigo, et al., Diamine derivative anti-Trichomonas vaginalis and anti-Tritrichomonas foetus activities by effect on polyamine metabolism, Biomed. Pharmacother. 95 (2017) 847–855, https://doi.org/10.1016/j.biopha.2017.09.007.
[192] M.M. Hoque, et al., Increased iron utilization and oxidative stress tolerance in a Vibrio cholerae flrA mutant confers resistance to amoeba predation, Appl. Environ. Microbiol. 89 (11) (2023) e0109523, https://doi.org/10.1128/aem.01095-23.
[193] C. d'Enfert, et al., The impact of the Fungus-Host-Microbiota interplay upon infections: current knowledge and new perspectives, FEMS Microbiol. Rev. 45 (3) (2021) fuaa060. ARTN.fuaa06010.1093/femsre/fuaa060.

[194] M.C. Fisher, D.W. Denning, The WHO fungal priority pathogens list as a game-changer, Nat. Rev. Microbiol. 21 (4) (2023) 211–212, https://doi.org/10.1038/s41579-023-00861-x.

[195] G.D. Brown, et al., Hidden killers: human fungal infections, Sci. Transl. Med. 4 (165) (2012) 165rv13, https://doi.org/10.1126/scitranslmed.3004404.

[196] E. Nikolaou, et al., Phylogenetic diversity of stress signalling pathways in fungi, BMC Evol. Biol. 9 (2009) 44, https://doi.org/10.1186/1471-2148-9-44.

[197] L. Valdés-Santiago, J.A. Cervantes-Chávez, J. Ruiz-Herrera, Ustilago maydis spermidine synthase is encoded by a chimeric gene, required for morphogenesis, and indispensable for survival in the host, FEMS Yeast Res. 9 (6) (2009) 923–935, https://doi.org/10.1111/j.1567-1364.2009.00539.x.

[198] A. Incharoensakdi, et al., Polyamines in cyanobacteria: biosynthesis, transport and abiotic stress response, Current research, technology and education topics in applied microbiology and microbial biotechnology 1 (2010) 23–32.

[199] D. Balasundaram, C.W. Tabor, H. Tabor, Oxygen toxicity in a polyamine-depleted spe2 delta mutant of Saccharomyces cerevisiae, Proc. Natl. Acad. Sci. U. S. A. 90 (10) (1993) 4693–4697, https://doi.org/10.1073/pnas.90.10.4693.

[200] M.K. Chattopadhyay, C.W. Tabor, H. Tabor, Polyamine deficiency leads to accumulation of reactive oxygen species in a spe2Δ mutant of Saccharomyces cerevisiae, Yeast 23 (10) (2006) 751–761, https://doi.org/10.1002/yea.1393.

[201] A. Kummasook, et al., Spermidine is required for morphogenesis in the human pathogenic fungus, Fungal Genet. Biol. 58–59 (2013) 25–32, https://doi.org/10.1016/j.fgb.2013.08.001.

[202] E. Koroleva, et al., Exploring polyamine metabolism of the yeast-like fungus, Emergomyces africanus, FEMS Yeast Res. 24 (2024) foae038, https://doi.org/10.1093/femsyr/foae038. ARTN foae038.

[203] T. Bicanic, T.S. Harrison, Cryptococcal meningitis, Br. Med. Bull. 72 (1) (2004) 99–118, https://doi.org/10.1093/bmb/ldh043.

[204] B. Toplis, et al., The virulence factor urease and its unexplored role in the metabolism of Cryptococcus neoformans, FEMS Yeast Res. 20 (4) (2020) foaa031, https://doi.org/10.1093/femsyr/foaa031.

[205] J.M. Kingsbury, et al., Novel chimeric spermidine synthase-saccharopine dehydrogenase gene (SPE3-LYS9) in the human pathogen Cryptococcus neoformans, Eukaryot. Cell 3 (3) (2004) 752–763, https://doi.org/10.1128/EC.3.3.752-763.2004.

[206] S.M. Levitz, D.J. DiBenedetto, R.D. Diamond, Inhibition and killing of fungi by the polyamine oxidase-polyamine system. Antifungal activity of the PAO-polyamine system, Antonie Leeuwenhoek 58 (2) (1990) 107–114, https://doi.org/10.1007/BF00422726.

[207] M.A. Pfaller, T. Gerarden, J. Riley, Growth inhibition of pathogenic yeast isolates by alpha-difluoromethylornithine: an inhibition of ornithine decarboxylase, Mycopathologia 98 (1) (1987) 3–8, https://doi.org/10.1007/BF00431009.

[208] M.A. Pfaller, J. Riley, T. Gerarden, Polyamine depletion and growth inhibition in Candida albicans and Candida tropicalis by alpha-difluoromethylornithine and cyclohexylamine, J. Med. Vet. Mycol. 26 (2) (1988) 119–126, https://doi.org/10.1007/BF00431009.

[209] E. Takahashi, et al., Spermidine-analogous triamines suppressed the growth of Candida albicans, Biol. Pharm. Bull. 36 (9) (2013) 1440–1447, https://doi.org/10.1248/bpb.b13-00148.

[210] J. Shen, et al., Mangiferin enhances the antifungal activities of caspofungin by destroying polyamine accumulation, Virulence 12 (1) (2021) 217–230, https://doi.org/10.1080/21505594.2020.1870079.

[211] Z. Liao, et al., Enhancement of the antibiofilm activity of amphotericin B by polyamine biosynthesis inhibitors, Int. J. Antimicrob. Agents 46 (1) (2015) 45–52, https://doi.org/10.1016/j.ijantimicag.2015.02.021.

[212] A. Greenland, D. Lewis, Amines in barley laves infected by brown rust and their possible relevance to formation of 'green islands', New Phytol. 96 (2) (1984) 283–291, https://doi.org/10.1111/j.1469-8137.1984.tb03565.x.

[213] D.R. Walters, M.A. Wylie, Polyamines in discrete regions of barley leaves infected with the powdery mildew fungus, erysiphe-graminis, Physiol. Plantarum 67 (4) (1986) 630–633, https://doi.org/10.1111/j.1399-3054.1986.tb05068.x.

[214] M. Rodríguez-Kessler, J.F. Jiménez-Bremont, Ustilago maydis induced accumulation of putrescine in maize leaves, Plant Signal. Behav. 4 (4) (2009) 310–312, https://doi.org/10.4161/psb.4.4.8089.

[215] Y.N. Zou, Q.S. Wu, K. Kuca, Unravelling the role of arbuscular mycorrhizal fungi in mitigating the oxidative burst of plants under drought stress, Plant Biol (Stuttg) 23 (Suppl 1) (2021) 50–57, https://doi.org/10.1111/plb.13161.

[216] Y.N. Zou, et al., Arbuscular mycorrhizal fungi regulate polyamine homeostasis in roots of trifoliate orange for improved adaptation to soil moisture deficit stress, Front. Plant Sci. 11 (2020) 600792, https://doi.org/10.3389/fpls.2020.600792.

[217] F. Kheyri, P. Taheri, S. Jafarinejad-Farsangi, Thiamine and induce bean resistance against : the role of polyamines in association with iron and reactive oxygen species, Biol. Control 172 (2022) 104955. ARTN.10495510.1016/j.biocontrol.2022.104955.

[218] F. Sommer, F. Bäckhed, The gut microbiota—masters of host development and physiology, Nat. Rev. Microbiol. 11 (4) (2013) 227–238, https://doi.org/10.1038/nrmicro2974.

[219] L.V. Hooper, A.J. Macpherson, Immune adaptations that maintain homeostasis with the intestinal microbiota, Nat. Rev. Immunol. 10 (3) (2010) 159–169, https://doi.org/10.1038/nri2710.

[220] M. Lyte, Microbial endocrinology in the pathogenesis of infectious disease, Microbiol Spectrum 4 (2) (2015), https://doi.org/10.1128/microbiolspec, 2016, VMBF-0021-2015.

[221] F. Sanchez de Medina, et al., Intestinal inflammation and mucosal barrier function, Inflamm. Bowel Dis. 20 (12) (2014) 2394–2404, https://doi.org/10.1097/MIB.0000000000000204.

[222] L.V. Hooper, D.R. Littman, A.J. Macpherson, Interactions between the microbiota and the immune system, Science 336 (6086) (2012) 1268–1273, https://doi.org/10.1126/science.1223490.

[223] G. Pontarollo, et al., Commensal bacteria weaken the intestinal barrier by suppressing epithelial neuropilin-1 and Hedgehog signaling, Nat. Metab. 5 (7) (2023) 1174–1187, https://doi.org/10.1038/s42255-023-00828-5.

[224] M.T. Sorbara, E.G. Pamer, Interbacterial mechanisms of colonization resistance and the strategies pathogens use to overcome them, Mucosal Immunol. 12 (1) (2019) 1–9, https://doi.org/10.1038/s41385-018-0053-0.

[225] T.I. Bui, et al., Modulation of gut microbiota metabolism in obesity-related type 2 diabetes reduces osteomyelitis severity, Microbiol. Spectr. 10 (2) (2022) e0017022, https://doi.org/10.1128/spectrum.00170-22.

[226] E.M. Schott, et al., Targeting the gut microbiome to treat the osteoarthritis of obesity, JCI Insight 3 (8) (2018), https://doi.org/10.1172/jci.insight.95997.

[227] C.W. Farnsworth, et al., Exacerbated Staphylococcus aureus foot infections in obese/diabetic mice are associated with impaired germinal center reactions, ig class switching, and humoral immunity, J. Immunol. 201 (2) (2018) 560–572, https://doi.org/10.4049/jimmunol.1800253.

[228] L. Ma, et al., Spermidine improves gut barrier integrity and gut microbiota function in diet-induced obese mice, Gut Microbes 12 (1) (2020) 1–19, https://doi.org/10.1080/19490976.2020.1832857.

[229] Q. Li, et al., Spermidine associated with gut microbiota protects against MRSA bloodstream infection by promoting macrophage M2 polarization, ACS Infect. Dis. 10 (11) (2024) 3751–3764, https://doi.org/10.1021/acsinfecdis.3c00669.

[230] M. Linsalata, et al., The influence of Lactobacillus brevis on ornithine decarboxylase activity and polyamine profiles in Helicobacter pylori-infected gastric mucosa, Helicobacter 9 (2) (2004) 165–172, https://doi.org/10.1111/j.1083-4389.2004.00214.x.

[231] G. Bruno, et al., Fecal Microbial Transplantation impact on gut microbiota composition and metabolome, microbial translocation and T-lymphocyte immune activation in recurrent Clostridium difficile infection patients, New Microbiol. 42 (4) (2019) 221–224. PMID: 31609455.

[232] Y. Zhang, et al., The altered metabolites contributed by dysbiosis of gut microbiota are associated with microbial translocation and immune activation during HIV infection, Front. Immunol. 13 (2022) 1020822, https://doi.org/10.3389/fimmu.2022.1020822.

[233] F. Madeo, et al., Spermidine: a novel autophagy inducer and longevity elixir, Autophagy 6 (1) (2010) 160–162, https://doi.org/10.4161/auto.6.1.10600.

[234] E. Sobieszczuk-Nowicka, et al., Dark-induced senescence of barley leaves involves activation of plastid transglutaminases, Amino Acids 47 (4) (2015) 825–838, https://doi.org/10.1007/s00726-014-1912-y.

[235] N. Minois, D. Carmona-Gutierrez, F. Madeo, Polyamines in aging and disease, Aging (Albany NY) 3 (8) (2011) 716–732, https://doi.org/10.18632/aging.100361.

[236] L. Imre, et al., Nucleosome destabilization by polyamines, Arch. Biochem. Biophys. 722 (2022) 109184, https://doi.org/10.1016/j.abb.2022.109184.

[237] M.K. Chattopadhyay, C.W. Tabor, H. Tabor, Absolute requirement of spermidine for growth and cell cycle progression of fission yeast (Schizosaccharomyces pombe), Proc. Natl. Acad. Sci. U. S. A. 99 (16) (2002) 10330–10334, https://doi.org/10.1073/pnas.162362899.

[238] M.A. Comini, Polyamine-based thiols in pathogens, in: Redox Chemistry and Biology of Thiols, Elsevier, 2022, pp. 555–584, https://doi.org/10.1016/B978-0-323-90219-9.00019-4.

[239] P. Nurse, What Is Life?: Understand Biology in Five Steps, David Fickling Books, 2020.

[240] P. McCann, Inhibition of Polyamine Metabolism: Biological Significance and Basis for New Therapies, Elsevier, 2012.

[241] A.S. Tyms, J.D. Williamson, C.J. Bacchi, Polyamine inhibitors in antimicrobial chemotherapy, J. Antimicrob. Chemother. 22 (4) (1988) 403–427, https://doi.org/10.1093/jac/22.4.403.

[242] A. Talevi, C. Carrillo, M. Comini, The thiol-polyamine metabolism of trypanosoma cruzi: molecular targets and drug repurposing strategies, Curr. Med. Chem. 26 (36) (2019) 6614–6635, https://doi.org/10.2174/0929867325666180926151059.

[243] K. El Bissati, et al., Novel synthetic polyamines have potent antimalarial activities in vitro and in vivo by decreasing intracellular spermidine and spermine concentrations, Front. Cell. Infect. Microbiol. 9 (2019) 9, https://doi.org/10.3389/fcimb.2019.00009.

[244] B.C. Mounce, et al., Inhibition of polyamine biosynthesis is a broad-spectrum strategy against RNA viruses, J. Virol. 90 (21) (2016) 9683–9692, https://doi.org/10.1128/Jvi.01347-16.

[245] C.J. Bacchi, et al., Novel synthetic polyamines are effective in the treatment of experimental microsporidiosis, an opportunistic AIDS-associated infection, Antimicrob. Agents Chemother. 46 (1) (2002) 55–61, https://doi.org/10.1128/AAC.46.1.55-61.2002.

[246] P.M. Tate, V. Mastrodomenico, B.C. Mounce, Ribavirin induces polyamine depletion via nucleotide depletion to limit virus replication, Cell Rep. 28 (10) (2019) 2620–2633, https://doi.org/10.1016/j.celrep.2019.07.099, e4.

[247] K. Sue, et al., Antimicrobial indole-3-carboxamido-polyamine conjugates target bacterial membranes and are antibiotic potentiators, Biomolecules 14 (3) (2024) 261, https://doi.org/10.3390/biom14030261.