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MINI-REVIEW

Acid-tolerant bacteria and prospects in industrial and environmental applications

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Abstract

Acid-tolerant bacteria such as *Streptococcus mutans*, *Acidobacterium capsulatum*, *Escherichia coli*, and *Propionibacterium acidipropionici* have developed several survival mechanisms to sustain themselves in various acid stress conditions. Some bacteria survive by minor changes in the environmental pH. In contrast, few others adapt different acid tolerance mechanisms, including amino acid decarboxylase acid resistance systems, mainly glutamate-dependent acid resistance (GDAR) and arginine-dependent acid resistance (ADAR) systems. The cellular mechanisms of acid tolerance include cell membrane alteration in *Acidithiobacillus thioxidans*, proton elimination by F_1–F_0–ATPase in *Streptococcus pyogenes*, biofilm formation in *Pseudomonas aeruginosa*, cytoplasmic urease activity in *Streptococcus mutans*, synthesis of the protective cloud of ammonia, and protection or repair of macromolecules in *Bacillus caldontenax*. Apart from cellular mechanisms, there are several acid-tolerant genes such as *gadA*, *gadB*, *adiA*, *adiC*, *cadA*, *cadB*, *cadC*, *speF*, and *potE* that help the bacteria to tolerate the acidic environment. This acid tolerance behavior provides new and broad prospects for different industrial applications and the bioremediation of environmental pollutants. The development of engineered strains with acid-tolerant genes may improve the efficiency of the transgenic bacteria in the treatment of acidic industrial effluents.

Key points

- *Bacteria tolerate the acidic stress by methylating unsaturated phospholipid tail*
- *The activity of decarboxylase systems for acid tolerance depends on pH*
- *Genetic manipulation of acid-tolerant genes improves acid tolerance by the bacteria*

Keywords Acid-tolerant bacteria · Acid tolerance mechanisms · Biofilm formation · Urease system · Bioremediation

Introduction

In the process of evolution, bacteria possess implicit mechanisms against different environmental stresses like acids, temperature, and antibiotics. Among all the extreme environmental conditions, the acidic environment is the most atypical environmental condition withstand by bacteria very often. Acid-tolerant bacteria are extremophiles that can tolerate a highly acidic environment which varies from pH 2.0 to pH 6.0. The acidic environments are formed either by natural processes or by anthropogenic activities. Acid mine drainage, marine volcanic vents, and acidic sulfur springs are the natural acidic environments. Among the anthropogenic activities, the wastewater discharged from industrial effluents also creates a favorable environment for different acid-tolerant bacteria to flourish (Nnadozie et al. 2017). Industrial effluents have a considerable amount of organic matter, suspended solids, organic nitrogen, as well as ammonia (Chowdhary et al. 2020). Industrial effluents have low pH which helps the different acid-tolerant bacteria to survive in stress conditions.

The acid-tolerant bacteria adopt different acid tolerance mechanisms such as physiological adaptation, metabolic responses, and proton-consuming mechanisms for their survival and growth (Kanjee and Houry 2013; Das et al. 2015). In the physiological adaptation, the outer membrane and periplasm of the bacteria must be altered since the outer membrane is adjacent to the external environment. To resist the acid stress, influx of protons is lowered by decreasing the fluidity of the membrane and changing the membrane composition (Feng

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et al. 2021). The concentrations of unsaturated lipids also decrease. The cyclopropane fatty acyl phospholipid synthase changes the structure of the unsaturated phospholipid tail. Moreover, outer membrane proteins (OMPs) can be blocked with the help of polyphosphate or cadaverine. HdeA and HdeB are two chaperone proteins that are reported to release the substrate protein with increased acid stress (Tapley et al. 2010). In *Escherichia coli*, Hsp31 is a homodimeric cytoplasmic chaperone that stabilizes the unfolded intermediates during stress. In addition to protein chaperones, there are DNA-binding *dps* that are also involved in acid stress by protecting the DNA in *Escherichia coli* (Calhoun and Kwon 2011). Apart from physiological adaptation, acid-tolerant bacteria also adopt metabolic responses for their survival.

In the case of metabolic responses to acid stresses, proton efflux occurs under mild stress and is mediated by the oxidative electron transport chain in *Escherichia coli* K-12 (Teelucksingh et al. 2020). The primary acid tolerance mechanism involves the direct utilization of intracellular protons. The cell membrane is the most significant part of bacteria, which mainly helps to survive in extremely harsh environments. In order to resist this harsh condition, solutes are transported across the cell membrane driven by primary ATP or with the help of a proton motive force involved in secondary transport systems (Kumar et al. 2020). Some acid-tolerant bacteria such as *Escherichia coli* and *Propionibacterium acidipropionici* can withstand a very low pH of 2.5 for several hours by maintaining their stationary phase by adopting various acid tolerance mechanisms (Cavero-Olguin et al. 2019; Guan and Liu 2020). Thus, different acid-tolerant bacteria adopt different adaptive modifications to resist acid tolerance and survive in stress conditions.

Acid tolerance mechanisms of the bacterial cells have wider applications in industrial bioprocesses, organic acid production, generation of microbial fuel cells, and biotreatment of industrial wastes. The wastewater contains a considerable amount of organic matter, and toxic heavy metals when discharged into the environment, causing water pollution, and severe health hazards to humans, animals, and plants present on the land surfaces in the vicinity of water bodies (Syam Babu et al. 2020). For this purpose, remediation is necessary to remove the harmful toxic elements present in the industrial discharge. The chemical treatment of wastewater includes various processes such as coagulation, precipitation, and oxidation (Yuan and Zhu 2016). However, the chemical treatment of wastewater is not eco-friendly due to sludge production, the generation of undesirable by-products, and the high amount of chemicals required for pH adjustment. Among various conventional techniques, bioremediation is the most modern approach. Bioremediation is an alternative approach to destroy and remediate more harmful contaminants to harmless contaminants using natural biological entities, primarily bacteria. The acid-tolerant bacteria have the potential to bioremediate the heavy toxic metals and metalloids present in the acid mine drainage or contaminated sludge (Syam Babu et al. 2020). Bioremediation of heavy metals by acid-tolerant bacteria includes various mechanisms such as biosorption, bioaccumulation, biodegradation, bioassimilation, biotransformation, and bioprecipitation (Hou et al. 2020). The acid-tolerant bacteria also degrade various petroleum hydrocarbon compounds, such as o-xylene, benzene, and toluene (Koul et al. 2021). This review aims to illustrate the different acid tolerance mechanisms of bacteria for sustaining at low pH. Various cellular and genetic mechanisms of acid tolerance and the evolution of these mechanisms have been discussed in detail. In addition, applications of acid-tolerant bacteria in industrial bioprocesses, microbial fermentation, microbial fuel cell, and environmental aspects such as bioremediation have been summarized. Genetic reprogramming strategies for improving acid tolerance have also been elaborated in this review.

Atypical environments of acid-tolerant bacteria

Acid-tolerant bacteria are extremophiles that thrive in extremely acidic environments around pH 5.0 and below. The acidic environments are formed either by natural processes or by anthropogenic influences, since the development of the industrial revolution. Acidic environments include acid mine drainage, marine volcanic vents, and acidic sulfur springs.

Atypical environments and ecosystems of acid-tolerant bacteria

Acid-tolerant bacteria sustain acidic environments where huge amounts of sulfur or pyrite are oxidized at a pH lower than 5.0. Sulfur and ferrous iron are oxidized aerobically to sulfuric acid and ferric iron respectively by acid-tolerant bacteria (Phyo et al. 2020). Mostly the acidic pyrite regions have been found around coal and sulfur mines. These regions mainly have an enhanced level of sulfide concentrations. Due to the presence of a significant amount of heavy metals and low organic matter, the coal and sulfur mines have low acidic niches $\leq$ pH 1.0 (Johnson and Quatrini 2020). There are several species of extremely acid-tolerant bacteria involved in this sulfate oxidation reaction, for example, *Sulfobacillus thermosulfidooxidans*, *Thiobacillus acidophilus*, and *Thiobacillus thiooxidans*. Large amounts of reduced sulfur are released from submarine volcanic areas and hydrothermal vents from magmatic sources which creates a favorable niche for acid-tolerant bacteria (Dopson and Johnson 2012). Among various metal-forming oxides zinc and copper, iron-forming sulfides are the most abundant sulfide minerals. The acid-tolerant bacteria including the member of

Acidithiobacillus sp., *Ferrimicrobium* sp., *Sulfobacillus* sp., *Acidimicrobium* sp., and *Leptospirillum* sp. can oxidize iron and sulfide minerals (Nural Yaman et al. 2020).

The pollution of municipal, agricultural land, and industrial discharge typically contains varying concentrations of organic and inorganic contaminants, such as dissolved heavy metals, xenobiotics, microplastic, and high concentrations of nitrates, phosphate, and total nitrogen. These organic and inorganic contaminants are responsible for the low pH of the wastewater and thereby form extremely acidic environments for the bacteria. *Acidophilus*, *Brevibacterium*, *Leptospirillum*, *Stenotrophomonas*, and *Thermogymnomonas* are extremely acid-tolerant bacteria that can resist the low pH of wastewater (Begum et al. 2022). The increasing evidence supports that acid mine drainage, marine volcanic vents, acidic sulfur springs, and industrial discharge are the favorable niche of acid-tolerant bacteria.

Role of acid-tolerant bacteria in the microbial ecology

Acid-tolerant bacteria are regarded as oligotrophic due to the low concentration of dissolved organic carbon in acidic environments. The chemolithoautotrophic acid-tolerant bacteria are present in deep mines, where there is no sunlight. Most bacteria that sustain acidic environments are chemolithoautotrophic and can oxidize sulfide and iron minerals (Hu et al. 2020a). The sulfur and iron oxidizing acid-tolerant bacteria are regarded as autotrophic, while others, which catalyze the dissimilatory oxidation of iron are either mixotrophic or else, are obligate heterotrophic. *Leptospirillum ferrooxidans* play a pivotal role in the iron cycle. It is an obligate chemolithoautotroph that can oxidize iron aerobically (Johnson et al. 2014). The members of the genera *Ferroplasma*, *Leptospirillum*, and *Acidithiobacillus* were present in the acid mines (Li et al. 2019). The genome sequencing of the *Acidithiobacillus* and *Leptospirillum* revealed the presence of a gene encoding nitrogen fixation enzyme.

The presence of heavy metals in the wastewater is responsible for the low pH; thus, the bacteria combat the acidic environments by producing urease enzyme (You et al. 2017). Urease plays a major role to neutralize the acid by producing alkali in the form of ammonia (NH_3), which in turn combines with the protons present within the cell resulting in the decrease of pH within the cell. The removal of NH_3 from the wastewater of industrial discharge is a two-step process, i.e., nitrification and denitrification (Martikainen 2022). Chemolithoautotrophic bacteria convert NH_3 into nitrite (NO_2^-) and nitrate (NO_3^-). The NO_3 ions are then converted to nitrogen (N_2) by the denitrification process (Jasmin et al. 2020). Thus, the primary source of nitrogen for acid-tolerant bacteria includes ammonia, nitrite, nitrate, and a few other dissolved organic nitrogen compounds. There are two independent enzymatic stages involved in the conversion of NO_3^- to NH_3. $NADH_2$-nitrate reductase catalyzes the reduction of NO_3^- to NO_2^-, and ferredoxin-nitrite reductase catalyzes the reduction of NO_2^- to NH_3. The reduction of nitrate to ammonia requires electrons; thus, a considerable amount of energy is required for the utilization of nitrate (Zhang et al. 2021). This study has proved that acid-tolerant bacteria are mainly chemolithoautotrophs or obligate heterotrophs. Different physical environments and physiological characteristics of acid-tolerant bacteria have been given in Table 1.

Cellular mechanisms of acid tolerance in bacteria

Acid-tolerant bacteria in the stationary phase can tolerate the low pH for several hours. Several bacteria have evolved different cellular mechanisms for sustaining the extremely acidic environment. When the bacteria encounter an acidic environment, the outer membrane and the periplasm are damaged as the outer membrane faces the external environment (Feng et al. 2021). After membrane bioenergetics, proton permeation, and lipid physiology is altered by the stress response which decreases the membrane fluidity and permeability of protons (Guan and Liu 2020). The cellular mechanisms of acid tolerance include cell membrane alteration, F_1–F_0–ATPase proton pump, biofilm formation, alkali production – urease activity, and protection or repairing of macromolecules.

Cell membrane alteration

The outer membrane conformation is mainly altered either in the fatty acyl chain or in the composition of the head group. The influx of proton is additionally decreased by obstructing the outer membrane proteins (OMPs) with polyphosphate or by cadaverine (Samartzidou et al. 2003). Polyphosphate anions (*polyP*) blocked the $PhoE_3$ porin and cadaverine blocked the $OmpC_3$ and $OmpF_3$ porins (Fig. 1a). In *Picrophilus oshimae*, the presence of rigid monolayer and the bulky isoprenoid core makes the proton impermeable (Van Villanueva et al. 2014). The acid-tolerant bacteria regulate membrane fluidity by changing the composition or structure of the fatty acid. To tolerate the acidic stress, cyclopropane fatty acyl phospholipid synthase (CFAS) decreases the concentration of unsaturated lipids and methylated the unsaturated phospholipid tail (Fig. 1b) (Qi et al. 2019).

For maintaining pH homeostasis, acid-tolerant bacteria use reverse membrane potential. In *Acidithiobacillus thiooxidans* and *Acidithiobacillus ferrooxidans*, there are abundant secondary transporters including H^+ATPase, symporters, and antiporters which help to maintain pH homeostasis (Li et al. 2019). *Picophilus torridus* and *Thermoplasma*

Table 1 Physical environments and physiological characteristics of acid-tolerant bacteria

Acid-tolerant bacteria	Energy sources	Carbon sources	Mode of nutrition	Oxygen requirement	pH range	Environment	References
Acidimicrobium ferrooxidans	Organic compounds	Yeast, organic compounds	Chemoorganoheterotropic	Aerobe	2.0 to < 2.4	Acid mine drainage	Huang and Jaffé 2018
Acidiphilium angustum	Organic compounds	Yeast, organic compounds	Photoorganoheterotropic	Obligate aerobe	0.5 to < 6.0	Sulfide sediment, coal mine	Ullrich et al. 2015
Acidiphilum cryptum	Organic compounds	Yeast, organic compounds	Chemoorganoheterotropic	Microaerobe	1.9 to 5.9	Coal refuse piles	Thomas et al. 2022
Acidophilum rubrum	Organic compounds	Organic compounds	Chemolithoheterotropic	Obligate aerobe	2.5 to < 6.0	Coal mine drainage	Hujslová et al. 2020
Acidiphilum symbioticum	Organic compounds	Organic compounds	Chemoorganoheterotropic	Obligate aerobe	1.5 to 5.0	Acid mine drainage	Singh et al. 2010
Acidobacterium capsulatum	Organic compounds	Organic compounds	Chemoorganoheterotropic	Aerobe	0.5 to 6.0	Sulfide sediment, metal deposits	Pankratov et al. 2012
Acidocella aminolytica	Organic compounds	Organic compounds	Chemoorganoheterotropic	Obligate aerobe	3.0 to 6.0	Copper mine	Kimoto et al. 2010
Alicylobacillus acidocaldarius	Organic compounds	Organic compounds	Chemoorganoheterotropic	Aerobe	2.5 to 5.0	Geothermal soil, hot spring	Salzano et al. 2022
Ferromicrobium acidophilus	Organic compounds	Organic compounds	Chemoorganoheterotropic	Anaerobe	1.3 to 4.8	Acid mine drainage	Sun et al. 2019
Flavobacterium acidurans	Sulfide compounds	Organic compounds	Chemoorganoheterotropic	Obligate aerobe	2.0 to < 5.0	Acid hot springs	Kang et al. 2013
Gallionella ferruginea	Iron compounds	Carbon dioxide	Chemolithoautotropic	Microaerobe	3.5 to 6.6	Fresh or marine water, hot spring	Bruneel et al. 2006
Leptospirillum ferrooxidans	Chalcopyrite, Ferrous disulfide compounds	Carbon dioxide	Chemolithohetrotropic	Aerobe	1.0 to < 3.0	Acid mine drainage, copper deposit	Harneit et al. 2006
Leptothrix discophora	Organic compounds, Iron compounds	Organic compounds	Chemoorganoheterotropic	Aerobe	0.5 to 6.5	River, pond, sulfide sediment	Santos and Johnson 2021
Metallogenium sp.	Iron compounds	Organic compounds	Chemoorganoheterotropic	Aerobe	3.5 to 6.0	Acid mine drainage	Narayanan et al. 2020
Rhodopila globiformis	Light, organic compounds	Organic compounds	Photoorganoheterotropic	Anaerobe	4.2 to 5.5	Acid sulfide spring	Ratnasari et al. 2021
Sulfobacillus thermosulfidooxidans	Sulfide compounds iron compounds	Carbon dioxide	Chemolithofacultativeautotropic	Obligate aerobe	1.9 to 3.0	Geothermal volcanic springs, sulfide ore	Liu et al. 2019
Thiobacillus acidophilus	Sulfide compounds	Carbon dioxide	Chemolithofacultativeheterotropic	Facultative aerobe	1.1 to 6.5	Acid mine drainage	Sriaporn et al. 2021
Thiobacillus ferrooxidans	Pyrite, sulfide compounds	Carbon dioxide	Chemolithoobligateautotropic	Obligate aerobe	1.0 to 6.0	Metal mine wastewater	Harneit et al. 2006
Thiobacillus intermedius	Sulfide compounds	Carbon dioxide	Chemolithofacultativeautotropic	Facultative aerobe	1.5 to 5.9	Fresh or marine water	Narayanan et al. 2020
Thiobacillus thiooxidans	Pyrite, tetrathionate, sulfide compounds	Carbon dioxide	Chemolithoobligateautotropic	Aerobe	0.5 to 5.5	Sulfide deposit, hot spring, acid mine drainage	Feng et al. 2015

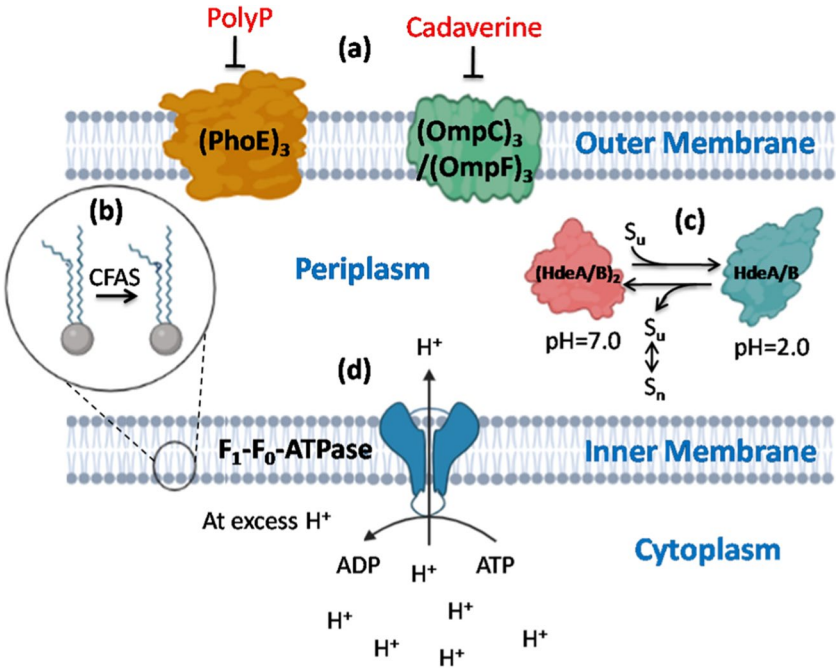

Fig. 1 Cell membrane alteration of acid-tolerant bacteria to acid stress. **a** Polyphosphate anions (PolyP) and cadaverine inhibit $(PhoE)_3$, i.e., outer membrane porin and $(OmpC)_3/(OmpF)_3$, respectively. **b** Cyclopropane fatty acyl phospholipid synthase (CFAS) methylated an unsaturated phospholipid tail. **c** At neutral pH, periplasmic protein HdeA/HdeB is dimeric and dissociates into unfolded monomer at pH 2.0. S_u is unfolded substrate and S_n is the native state configuration. **d** Proton pump F_1–F_0–ATPase is an acid tolerance system helps in maintaining pH homeostasis by removing out excess H^+ from the cytoplasm

acidophilum sustain the acidic environment due to the presence of those secondary transporters which regulate the acidic environment by using the transmembrane electrochemical gradient of protons for active transport (Futterer et al. 2004). The size, as well as the permeability of the membrane channels, are important mechanisms for maintaining pH homeostasis. In *Acidithiobacillus ferrooxidans*, due to the change in pH from pH 3.5 to pH 1.5, the outer membrane protein (Omp40) is upregulated (Shu and Huang 2022). Omp40, a large external L3 loop regulates both the size and the ion selectivity at the porin entrance. Organic acids including acetic acid and lactic acid are harmful to acid-tolerant bacteria. These protonated acids having dissociable protons can pass easily through the cell membrane. The genome of *Picophilus torridus* revealed genes encoding the degradation pathway of organic acid (Futterer et al. 2004). These genes encode the enzymes propionyl-CoA synthase, two acetyl-CoA synthetases, and lactate-2-monooxygenase that transform lactate into pyruvate.

HdeA and HdeB are two periplasmic chaperones that can tolerate acidic stress (Mates et al. 2007). The primary function of HdeA is to prevent the acid-induced accumulation of proteins and help in the dissolving and renaturation of the protein (Malki et al. 2008). HdeB is another acid stress chaperone that has similar functions to HdeA (Fig. 1c). In *Escherichia coli*, heat shock cytoplasmic chaperone, Hsp31 bind and stabilize the unfolded protein intermediates during the acid stress, and thereafter allows the protein to refold spontaneously or with the help of ATP-dependent chaperone (Mujacic et al. 2004). In an acidic environment DNA-binding Dps protein protects DNA during acid stress (Arcari et al. 2020). Thus, the acid-tolerant bacteria alter lipoidal cell membrane, and morphology to encounter acid stresses because of maintaining the proper cell membrane structure and function which is vital for all cellular metabolic activities.

F_1–F_0–ATPase proton pump

Proton motive force (PMF) estimates the proton gradient inside the cell which is produced due to the charge separation between the cytoplasm and the outer environment. PMF-dependent proton pump is another acid tolerance system in the bacteria that plays a pivotal role in maintaining pH homeostasis (Shu and Huang 2022). In an acidic environment, the accumulation of H^+ decreases the internal pH, and then the proton pump begins ATP consumption (Fig. 1d) (Sun 2016). Therefore, any protons that pass through the F_1–F_0–ATPase for the cell reduce the molecular oxygen at the terminal oxidase, resulting in the cessation of metabolism. *Sulfolobus acidocaldarius* survives the acidic pH by extruding the protons from the cell through F_1–F_0–ATPase (Hu et al. 2020b). In several acid-tolerant bacteria like *Streptococcus pneumonia* and *Lactobacillus acidophilus*, the F_1–F_0 operon is transcribed due to encounters with acidic pH (Martín-Galiano et al. 2001; Xu et al. 2022). *Streptococcus mutans* encounters acid stress by upregulating the F_1-F_0-ATPase (Kuhnert et al. 2004). Hence, the acid-tolerant bacteria tolerate the outside acidity and maintain pH homeostasis by removing excess H^+, catalyzing ATP hydrolysis through the F_1–F_0–ATPase proton pump. Apart from cell membrane alteration and removing excess H^+

through F_1–F_0–ATPase, acid-tolerant bacteria form biofilm in response to environmental stresses to prevent the inflow of H^+. Thus, the acid-tolerant bacteria withstand the acidic environment by forming surface attached communities.

Biofilm formation

Several bacteria withstand the acid stress by growing as a community irreversibly attached to a surface by forming biofilm (Liu et al. 2019). There are various acid tolerance mechanisms in bacteria, but biofilm formation is unique as it involves communication within the community of the cells (Guo et al. 2021). In some organisms, biofilm act as a strong tolerance to an acidic environment, whereas their planktonic cells are acid-sensitive (Welin-Neilands and Svensater 2007). Biofilm act as strong tolerance to acid stress because some proteins are only expressed when the biofilm is formed. In *Pseudomonas aeruginosa*, *vfr* and *gacA* are the biofilm-forming genes that regulate the *luxR* homolog, *lasR*. *lasR* activates *lasI* expression, producing 3-oxo-C12-HSL which binds to the receptor protein LasR to form a complex and regulates the biofilm formation (Fig. 2a). The negative regulator, *rsaL,* prevents *lasR* (Williams and Camara 2009). This LasR protein-AHL complex positively drives the expression of multiple structural genes associated with biofilm formation, pathogenicity, and secondary metabolism. In *Streptococcus mutans*, *luxS* synthesizes AL2, which is secreted extracellularly, and *luxS* also repressed transcription of *irvA* (Elango et al. 2021). However, when the cell encounters acid stress, the expression of the *irvA* gene increased dramatically. The overexpression of *irvA* causes the repression of *mutA* and *mutR* transcription (Fig. 2b).

The quorum-sensing system of *Streptococcus mutans* regulates the biofilm formation and acts as acid tolerance. The

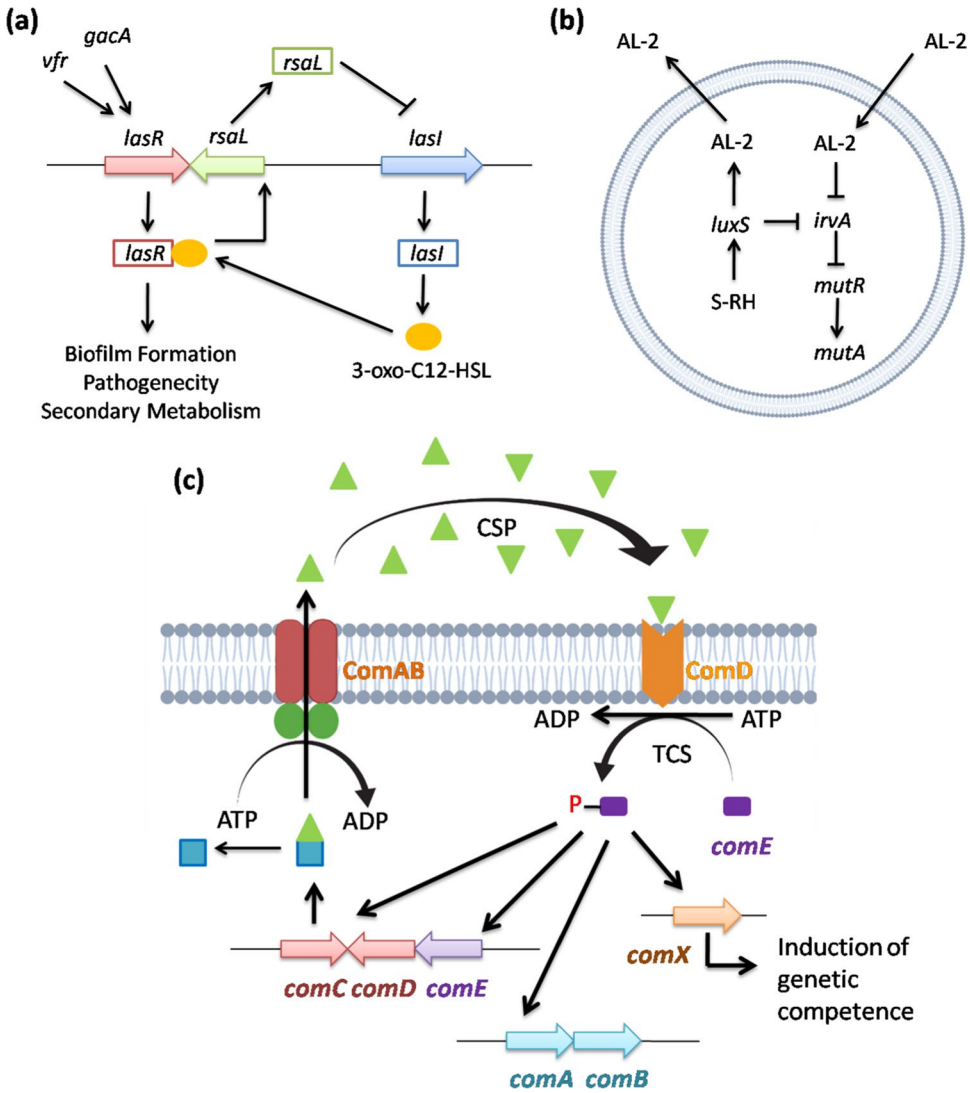

Fig. 2 Biofilm formation is one of the acid tolerance mechanisms. **a** In *Pseudomonas aeruginosa*, *vfr* and *gacA* regulate the *lasR* which in turn activates *lasI* expression. *lasI* produces 3-oxo-C12-HSL which binds to the receptor protein LasR to form a complex and regulates the biofilm formation. **b** *luxS* synthesizes AI-2 in *Streptococcus mutans* which is secreted outside of the cell induces biofilm formation. *luxS* in turn repressed transcription of *irvA*. High levels of *irvA* cause the repression of *mutA* and *mutR* transcription. **c** In *Streptococcus mutans*, the signaling peptide or CSP induces a quorum-sensing cascade which activates the production of bacteriocins and genetic competence *comC*, *comD*, *comE*

competence stimulating peptide (CSP) is produced when the ABC transporter, encoding the gene c*omAB* export permease which thereby cleaves the product of the *comC* gene (Guo et al. 2021) (Fig. 2c). After reaching the critical density, CSP is ascertained by sensor kinase, ComD (encoded by *comD*), which phosphorylates the *comE* and initiates the transcription of an alternate sigma factor, *comX* (Bikash and Tal-Gan 2019). In *Streptococcus pneumonia*, phosphorylated *comE* activates two competence-specific operons, *comAB* and *comCDE*, and the *comX* gene. The *comX* gene helps in inducing genetic competence and other cell density-dependent phenotypes (Guo et al. 2021). Environmental stresses like low pH and nutrient depletion modulate the level of CSP. The interaction with ComD is also modulated, affecting the regulation of *comAB*, *comCDE* operon, and *comX* gene. Thus, bacterial cells can ensure their survival in various harmful extreme environments by forming biofilms.

Alkali production—urease activity

Acid-tolerant bacteria can also neutralize the acidic environment by producing alkaline compounds during extracellular metabolism. Urea is hydrolyzed by ureases to ammonia and carbon dioxide (CO_2) (Fig. 3) (Sedghi et al. 2021). The urease plays an essential role in neutralizing the acid by producing alkali in the form of ammonia, which integrates with the protons present inside the cell and thus decreases the internal pH (Zhou and Fey 2020). The urease system comprises of *ureIABCEFGD* operon (Cotter and Hill 2003). Acid-tolerant bacteria can resist acid tolerance at a very low pH of 2.5 by regulating the urease system. In an acidic environment, the gene *ureI* in *Helicobacter pylori* and *Streptococcus salivarius* helps in transporting urea from outside to the cytoplasm (Griswold et al. 2004). Thus, the urease enzyme protects the cells from an acidic environment by producing an alkaline product, ammonia. *Streptococcus sanguis* and *Streptococcus suis* withstand an acid stress environment with the help of urease enzyme activity (Kanjee and Houry 2013; Gruening et al. 2006). Thus, the urease system plays a significant role by protecting its cellular components in acid stress conditions. Malolactic fermentation is another method of alkali production by *Streptococcus mutans* and *Oenococcus oeni* (Sedghi et al. 2021). They survive in acid stress through the process of alkali production inside the cytoplasm. During alkali production, CO_2 is produced as a by-product. Afterward, the produced CO_2 diffuses out from the cytoplasm. Thus, the mechanism of alkali production is an efficient method for the survival of acid-tolerant bacteria in an acid stress environment.

Protection or repairing of macromolecules

In acid stress conditions, the stability of membrane protein is a very important factor (Kim et al. 2021). Specific proteins are induced in these conditions to protect the DNA and proteins of acid-tolerant bacteria. Macromolecules in particular *dps* and *recA* are impaired and lose their function. In an acidic environment, *dps* protects DNA binding in a cage-like structure with iron sequesters and reduced hydrogen peroxide detoxification (Calhoun and Kwon 2011). *recA* is the major factor in repairing DNA molecules and activates the SOS response in acidic stresses (Adikesavan et al. 2011). *Oenococcus oeni* has Lo18, a heat shock protein that enhances the acid tolerance capability of bacteria by reducing protein aggregation, and thus it stabilizes the membrane and protects the proteins in acid stress conditions (Weidmann et al. 2017; Matsumoto et al. 2022). *Ffh* is also another essential component involved in the translocation

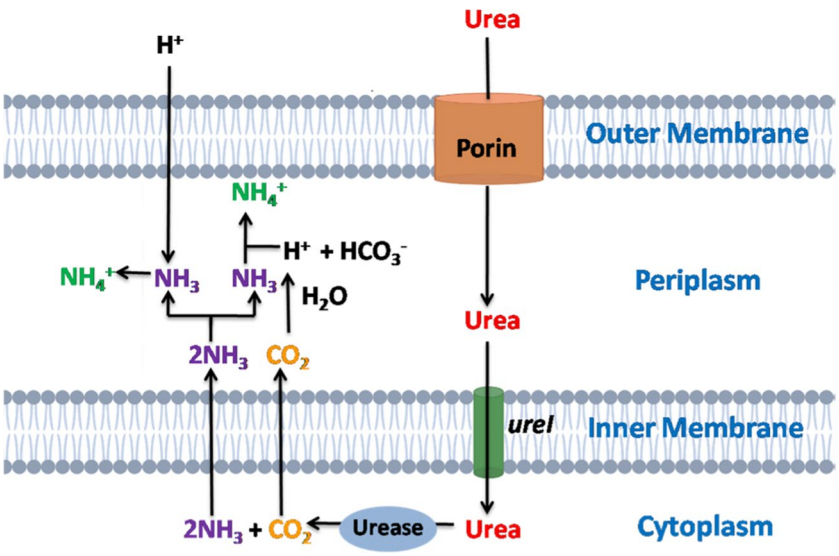

Fig. 3 Acidic environment can be neutralized by producing alkaline compounds during extracellular metabolism. The urease system helps in neutralizing the acid by producing alkali in the form of ammonia, which combines with the protons present inside the cell and thus decreases the internal pH. Urea the major substrate of alkali production enters from outside to the periplasm through porin and the cytoplasm through *ureI*, which then catabolized to ammonia and carbon dioxide by ureases in the cytoplasm. The gases diffuse rapidly to the periplasm which forms NH_4^+ and HCO_3^-

of protein pathways within the membrane and also helps in protein transport outside the cell (Mishra et al. 2019). In acid stress conditions, many other chaperones like DnaK, DnaJ, GroEL, GroES, GrpE, Clp proteases, and EF-Tu help in repairing the proteins as molecular chaperones (Shabayek and Spellerberg 2017). Acid-induced DNA damage is repaired with the help of *uvrABCD*, DNA polymerase, and DNA ligase. In *Streptococcus mutans*, *uvrA* repairs the DNA damage during acid stress at a pH of 5.0. Proteins like DnaK from *Escherichia coli* and IrrE from *Deinococcus radiodurans* also take part in DNA repair mechanisms during acid stress (Gaougaou et al. 2020). In *Bacillus caldontenax*, *uvrA* and *uvrB* helps in the recognition of DNA cooperative damage (Ghodke et al. 2020). Thus, different mechanisms of acid tolerance efficiently work together for the survival and proper metabolism of acid-tolerant bacteria in an acidic stress environment. Some acid-tolerant bacteria employ more than one tolerance mechanism for maintaining homeostasis. However, some acid-tolerant bacteria can also alter only the membrane bioenergetics and membrane fluidity for survival in hostile conditions.

Genetic mechanisms of acid tolerance in bacteria

Apart from cellular interaction, acid-tolerant bacteria tolerate the acidic environment with the help of acid-tolerant genes. The acid-tolerant genes that control the acid-tolerant mechanisms have been given in Table 2. There are four different pyridoxal-5'-phosphate (PLP) dependent amino acid decarboxylase acid resistance (AR) systems for acid tolerance. These acid resistance systems include glutamic acid-dependent acid resistance (GDAR) system, arginine-dependent acid resistance (ADAR) system, lysine-dependent acid resistance (LDAR) system, and ornithine-dependent acid resistance (ODAR) system.

Table 2 The acid-tolerant genes controlling different acid tolerance mechanisms

Acid-tolerant bacteria	Acid-tolerant genes	Mechanisms	Reference
Escherichia coli	*gadA/B*	Convert glutamate to GABA.	Ma et al. 2012
Lactobacillus reuteri	*gadC*	Exchange extracellular glutamate inside and intracellular GABA outside.	Yogeswara et al. 2020
Escherichia coli	*ybaS*	Glutamine is transformed into glutamate and ammonia.	Lu et al. 2013
Escherichia coli	*adiC*	Exchange extracellular arginine inside and intracellular agmatine outside.	Kanjee and Houry 2013
Escherichia coli	*arcD*	Arginine is transported intracellularly.	Guan and Liu 2020
Escherichia coli	*cadB*	Exchange extracellular lysine inside and intracellular cadaverine outside.	Ma et al. 2015
Escherichia coli	*speF*	Convert ornithine to putrescine.	Kanjee and Houry 2013
Escherichia coli	*potE*	Exchange extracellular ornithine inside and intracellular putrescine outside.	Guerra et al. 2018
Pseudomonas aeruginosa	*lasR*	Stimulate the biofilm formation.	Williams and Camara 2009
Streptococcus mutans	*luxS*	*luxS* mediated quorum sensation regulates the emergence of biofilm.	Wen and Burne 2004
Lactobacillus acidophilus *Streptococcus mutans*	F_1–F_0 –ATPase	Removes out excess H^+ catalyzing ATP hydrolysis.	Martín-Galiano et al. 2001; Kuhnert et al. 2004
Helicobacter pylori	*recA*	DNA repair and activates SOS response.	Adikesavan et al. 2011
Streptococcus mutans	*uvrA*	Repair DNA damage by nucleotide-excision repair.	Zheng et al. 2018
Lactococcus lactis	*dnaK*	Regulates the expression of heat shock genes in the response to protein misfolding.	Abdullah-Al-Mahin et al. 2010
Escherichia coli	*hdeA/hdeB*	Prevent the acid-induced aggregation of proteins and helped in the dissolving and renaturation of the protein.	Malki et al. 2008
Acidocella sp. *Acidiphilium facilis*	*nahA, nahG, nahH*	Degrade the petroleum hydrocarbons, such as toluene, naphthalene, phenanthrene, and anthracene.	Koul et al. 2021
Pseudomas putida	*toMO*	Biodegradation of petroleum hydrocarbon compounds, such as o-xylene, benzene, and toluene.	Miri et al. 2021

Acid-tolerant operon/genes in various bacteria

All four different pyridoxal-5'-phosphate (PLP) dependent amino acid decarboxylase acid resistance (AR) systems competently work together for optimal metabolism and growth of the acid-tolerant bacteria in a harsh low pH environment. Some acid-tolerant bacteria use one of the acid-tolerance systems to sustain the acid stress while some use more than one acid tolerance system (Du et al. 2019). The GDAR and ADAR systems can operate under extreme acid stress whereas the LDAR system and the ODAR system operate most effectively under mild acid stress.

Glutamic acid-dependent acid resistance (GDAR) system The GDAR system has two Gad enzymes encoded by the *gadA* and *gadB* genes and one glutamate/γ-aminobutyric acid (GABA) antiporter encoded by the *gadC* gene (Ma et al. 2012). The antiporter GadC exchange extracellular protonated glutamate inside and intracellular GABA outside. Due to the exchange between glutamate and GABA, protons are consumed inside the cells. Thus, the intracellular pH increases, thereby protecting the cell from acid shock (Fig. 4a) (Ma et al. 2012). In *Lactobacillus reuteri*, antiporter GadC transports out GABA with glutamate exchange (Yogeswara et al. 2020). The antiporter GadC also transports glutamine inside the cell, which is transformed into glutamate and ammonia with the help of the acid-activated *ybaS* gene. In *Escherichia coli*, acid-activated glutaminase, the *ybaS* gene, converts L-glutamine to L-glutamate and neutralizes H^+ by producing ammonia (Lu et al. 2013). *gadX* and *gadW* mainly regulate the GADR system. *Escherichia coli* can sustain this low pH with the help of a regulatory protein, encoded by the *yhiF* gene, and a lipoprotein Slp. (Mates et al. 2007). This suggests that *gadB* and *gadC* are the primary genes that help in the conversion of glutamate to GABA. The activity of *gadB* and *gadC* is regulated by all the genes including *gadA*, *gadX*, *gadW*, *gadE*, *hdeA*, *hdeD*, *yhiD*, *yhiF*, and *slp*. Hence, all the genes maintain pH

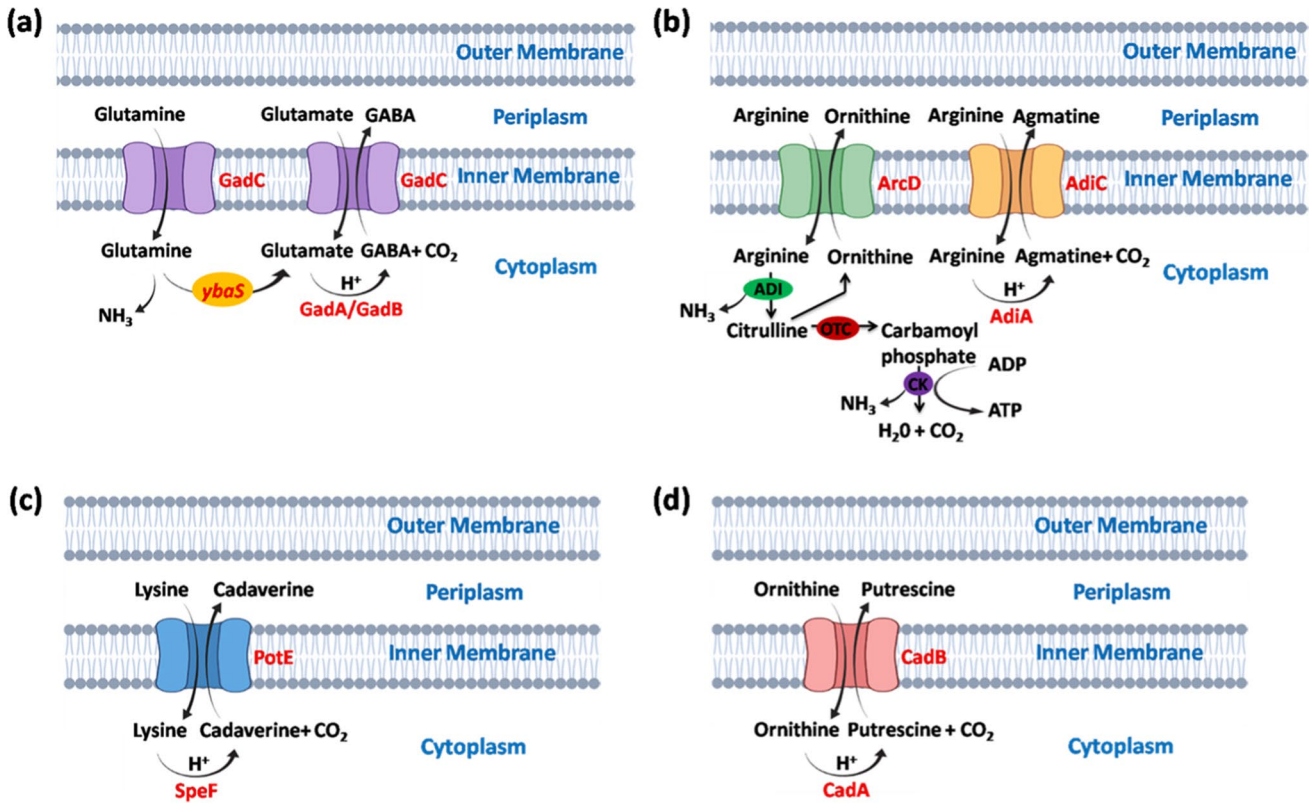

Fig. 4 A schematic illustration of the different acid resistance mechanisms. **a** Glutamic acid-dependent acid resistance (GDAR) system. Antiporter GadC exchanges extracellular glutamate inside and intracellular GABA outside. GadA and GadB convert glutamate to GABA. Glutamine also transported by GadC is transformed into glutamate and ammonia with the help of protein encoded by the *ybaS* gene. **b** Arginine-dependent acid resistance (ADAR) system. Antiporter AdiC exchange extracellular arginine inside and exchange intracellular agmatine outside. AdiA converts arginine to agmatine. Arginine is also transported inside by ArcD and then ADI converted it to citrulline and ammonia. OTC catalyzes citrulline to ornithine and carbamyl phosphate which is finally converted to ammonia by CK. **c** Lysine-dependent acid resistance (LDAR) system. Antiporter CadB exchanges extracellular lysine inside and intracellular cadaverine outside. CadA converts lysine to cadaverine. **d** Ornithine-dependent acid resistance (ODAR) system. Antiporter PotE exchange extracellular ornithine inside and intracellular putrescine outside. SpeF converts ornithine to putrescine

homeostasis. The GDAR system helps several acid-tolerant bacteria to sustain in an extremely acidic environment as low as pH 2.0.

Arginine-dependent acid resistance (ADAR) system The ADAR system is induced maximally in acidic conditions, generally at pH ~ 5.0, and this mechanism takes place in acid-tolerant bacteria that grow in anaerobic conditions (Bearson et al. 2009). *adiA* gene encoding the cytoplasmic inducible arginine decarboxylase, *adiY*, the regulatory gene, and the antiporter encoding *adiC* gene regulates the ADAR system. Arginine, which enters the cell through the antiporter AdiC, is transformed into agmatine through catalysis. AdiA mediates the conversion of arginine to agmatine (Fig. 4b) (Kanjee and Houry 2013). Then this agmatine again moves outside of the cell. Due to this exchange process, intracellular protons are consumed. In *Escherichia coli*, antiporter AdiC helps in the exchange of extracellular arginine inside and intracellular agmatine outside (Kanjee and Houry 2013). Moreover, the ADAR system is also regulated by antiporter ArcD. Arginine enters the cell by ArcD, and after that, arginine is metabolized to ammonia and citrulline by ADI (Guan and Liu 2020). Then the citrulline is phosphorylated to ornithine and carbamoyl phosphate is phosphorylated by ornithine carbamoyltransferase (OTC). The ornithine is transported out of the cell, thereafter, carbamyl phosphate is transformed into ammonia and carbon dioxide by carbamate kinase (CK). This exchange from carbamyl phosphate to ammonia and carbon dioxide yields ATP (Shabayek and Spellerberg 2017). In *Streptococcus pyrogens*, the ADAR system is the major defense mechanism against acid stress (Hirose et al. 2021). Hence, the ADAR system is also one of the efficient mechanisms for tolerating acid-tolerant bacteria in acidic stresses.

Lysine-dependent acid resistance (LDAR) system The LDAR system is induced at pH 5.5 in anaerobic conditions. The *cadBA* operon consists of *cadA* and *cadB* genes, regulated by the *cadC* gene product (Du et al. 2021). *cadC* induces *cadBA* operon by interacting among the transmembrane helix and the lysine-specific permease, *lysP* (Brameyer et al. 2020). In *Escherichia coli*, membrane-integrated transcriptional activator *cadC* can indirectly sense lysine with the interaction of *lysP* (Martini et al. 2021). Lysine enters inside the cell by antiporter CadB which is then converted to cadaverine by CadA within the cell, and transported outside by CadB (Fig. 4c). In *Escherichia coli*, antiporter CadB helps in the exchange of extracellular lysine inside and intracellular cadaverine outside (Ma et al. 2015). In *Edwardsiella tarda*, *cadBA* operon was identified which helps to sustain low pH (Du et al. 2021). Thus, CadB is a transmembrane protein having a significant homology with the lysine antiporter.

Ornithine-dependent acid resistance (ODAR) system: In the ODAR system, two genes, *speF* and *potE* are induced at low pH. Ornithine enters the cell by antiporter PotE, converted to putrescine within the cell, and then transported outside by PotE (Fig. 4d). In *Escherichia coli*, antiporter PotE exchanges extracellular ornithine inside and intracellular putrescine outside (Guerra et al. 2018). All the decarboxylases have optimal enzyme activities and are specific at a particularly low pH. For example, *gadA*/*gadB* is specific between pH 1.7 and pH 2.8, *adiA* is specific between pH 4.9 and pH 5.2, *ldcI* is specific at pH 5.7, and *speF* is specific at pH 6.5 (Foster 2004). Hence, the acid-tolerant bacteria can show a robust acid stress response at a pH that varies between pH 4.0 and pH 7.0, and the enzyme activity decreases with the increase in pH. Therefore, the ability of the acid resistance systems to resist extreme acid stress depends on the pH range of the decarboxylases. So, according to the pH range, the efficiency of decarboxylase systems is as follows GDAR > ADAR > LDAR >> ODAR. The acid-tolerant decarboxylase systems evolved gradually from simpler to complex operon systems depending on the acidic environment encountered by the acid-tolerant bacteria.

Evolution and diversity of acid-tolerant genes and bacteria

In order to tolerate the highly acidic environment, different acid-tolerant bacteria developed different mechanisms of acid tolerance. The acid-tolerant genes also evolved gradually from *Streptococcus mutans*, the first acid-tolerant bacteria discovered in 1924 (Xiao et al. 2016). In the acidic environment, the cytoplasm became acidified, as a result of which the protein and DNA molecules were structurally damaged. Due to the damage of the protein and DNA molecules, protein-repair chaperon DnaK was synthesized resulting in the expression of the signal recognition gene, *ffh*. This *ffh* increased amino acid metabolism, and ammonia production by the ADI pathway, which thereby induces of H^+-ATPase, and upregulation of the protein regulating DNA damage, RecA (Liu et al. 2015). Moreover, *Streptococcus mutans* endure the acidic environment by forming biofilm. The quorum-sensing system *irvA* and *luxS* regulate the biofilm formation and act for acid tolerance (Yoshida et al. 2005). The proteomic analysis of both the biofilm and planktonic phase of *Streptococcus mutans* indicated that 57 proteins were over-expressed in the biofilm system (Qayyum et al. 2019). This result showed that biofilm is tolerant to low pH environments. In *Streptococcus pyogenes*, the ADAR system is the primary defense mechanism against acid stresses (Liu et al. 2015). Thus, the *arc* operon comprises the genes of *adiA*, *adiY*, and *adiC* which is the primitive operon system for tolerating acid stress maximally. Along with the ADAR system, F_1–F_0–ATPase also acts as the defense

mechanism of acid tolerance in *Streptococcus pyogenes*. Thus, acid-tolerant bacteria evolve to use more than one acid tolerance mechanism to sustain the acidic environment.

Streptococcus enterica survives at a low pH with the help of the ADAR and LDAR system of acid tolerance (Du et al. 2021). Therefore, the *cadBA* operon evolved after the *arc* operon. The genes *cadA*, *cadB*, and *adiA* encoding lysine decarboxylase, lysine–cadaverine antiporter, and arginine decarboxylase, respectively, are involved in acid tolerance mechanisms. In *Salmonella enterica*, *rpoS* act as stress tolerance, and the *ydcI* gene control the *rpoS* regulation (Romiyo and Wilson 2020). *ydcI* gene is also involved in the biofilm formation, therefore it prevents the *Salmonella enterica* from any type of acid stress. A recent study showed that the operons regulating acid tolerance are comparatively much more complex with various genes such as *gadA*, *gadB*, and *gadC. gad* operon can sustain very low acid stress as low as below pH 2. All these acid tolerance mechanisms competently work together for optimal metabolism and growth of the acid-tolerant bacteria in a harsh low pH environment. These acid-tolerant operon systems have been identified in a huge variety of bacterial species and are widely distributed. The evolution and diversity of the acid-tolerant genes in the bacterial species are mainly governed by horizontal gene transfer and recombination, and all the operon systems evolved from simpler systems to extensively dispersed complex systems.

Applications of acid-tolerant bacteria in industrial bioprocesses and bioremediation

Acid tolerance mechanisms of the bacterial cells have wide applications in various aspects like in industrial bioprocesses and also in the biotreatment of industrial wastes, mainly mine effluents and oil spills (Feng et al. 2021) (Fig. 5). Acid tolerance mechanisms are also used for improving organic acid production. The development of effective tools for improving the acid tolerance mechanism is important for enhancing the applications of industrial acid-tolerant bacteria.

Acid-tolerant strains in industrial bioprocesses and generating bioelectricity

Acid-tolerant bacteria have a huge contribution to the production of industrial bioprocesses. During industrial production of lactic acid fermentation with *Lactobacillus*, acid is produced in the fermentation chamber. Thus, *Lactobacillus* adopts several mechanisms to resist the severe acid stress conditions during the process of fermentation. In *Lactobacillus*, acid-tolerant mechanisms include macromolecular repair and a glutaminase-dependent acid resistance system (Cui et al. 2020). In lactic acid acid-tolerant bacteria, low pH activates the glutamate decarboxylase system, which thereby enhances the production of GABA (Lyu et al. 2018). Thus, high GABA production is used for screening lactic acid bacteria. *Lactobacillus reuteri* sustains in the lactic acid using glutamate decarboxylase system in which GadA/GadB converts glutamate to GABA that is transported outside by GadC (Cui et al. 2020). Apart from the glutamate decarboxylase system, *Lactobacillus lactis* tolerates the acid by decreasing the intracellular protons and transferring extracellular H^+ followed by consumption of intracellular H^+. The transfer of extracellular H^+ results in a change in the cell membrane and solidification of the cell wall. The consumption of intracellular H^+ includes decarboxylation and the generation of alkali compounds. The protons are removed from the cell through F_1-F_0-ATPase which in turn produces ATPs (Zhang et al. 2016). Molecular chaperones GroES and GroEL protein help the *Lactobacillus lactis* to survive in acid stress. *murG* gene improves the lactic acid tolerance of *Lactobacillus lactis* by changing the cell membrane constituents. In addition, *gshA* and *gshB* help in acid tolerance by changing the metabolic regulation of *Lactobacillus lactis* (Guan and Liu 2020). Thus, all these genes improved acid tolerance through genetic manipulation in the genetically engineered bacteria.

In the industrial manufacturing of acetic acid and butyric acid, fermentative bacteria are also highly tolerant of acidic environments (Winfield and Groisman 2003). *Clostridium tyrobutyricum* immobilized in a fibrous bed bioreactor (FBB) produces a higher concentration of butyric acid (Wainaina et al. 2019). This fermentative bacterium survives by developing different indigenous genetic systems such as *gadA*, *gadB*, and *gadC* to resist the bacterial cells against acid stress conditions. Thus, the GDAR system plays a major role in *Clostridium tyrobutyricum* to sustain butyric acid. RNA-Seq transcriptomic study of *Acetobacter pasteurianus* was analyzed for identifying the acid tolerance mechanisms during acetic acid production (Yang et al. 2019). *Acetobacter pasteurianus* sustains an acidic environment with help of the *uvrA* gene which helps in macromolecule protection and repair. The omics study analyzed that *Acetobacter acetate* tolerates the acetic acid with the help of *yro2* and *mrh1* which help in cell membrane modification. Also, *COX20*, PEP*3*, and *RTT109* protect *Acetobacter acetate* against acetic acid (Sakuntala and Kim 2022). Propionic acid is the commonly used organic acid used for the synthesis of herbicides, cellulose fiber, and paint. *Propionibacteria* can synthesize propionic acid by using the transcarboxylase enzyme (Piwowarek et al. 2018). *Propionibacteria acidipropionici* sustains the highly acidic propionic acid with the help of the GDAR system and ADAR system. Thus, all the genes including *gadB*, *ybaS*, *arcA*, and *arcC* regulate

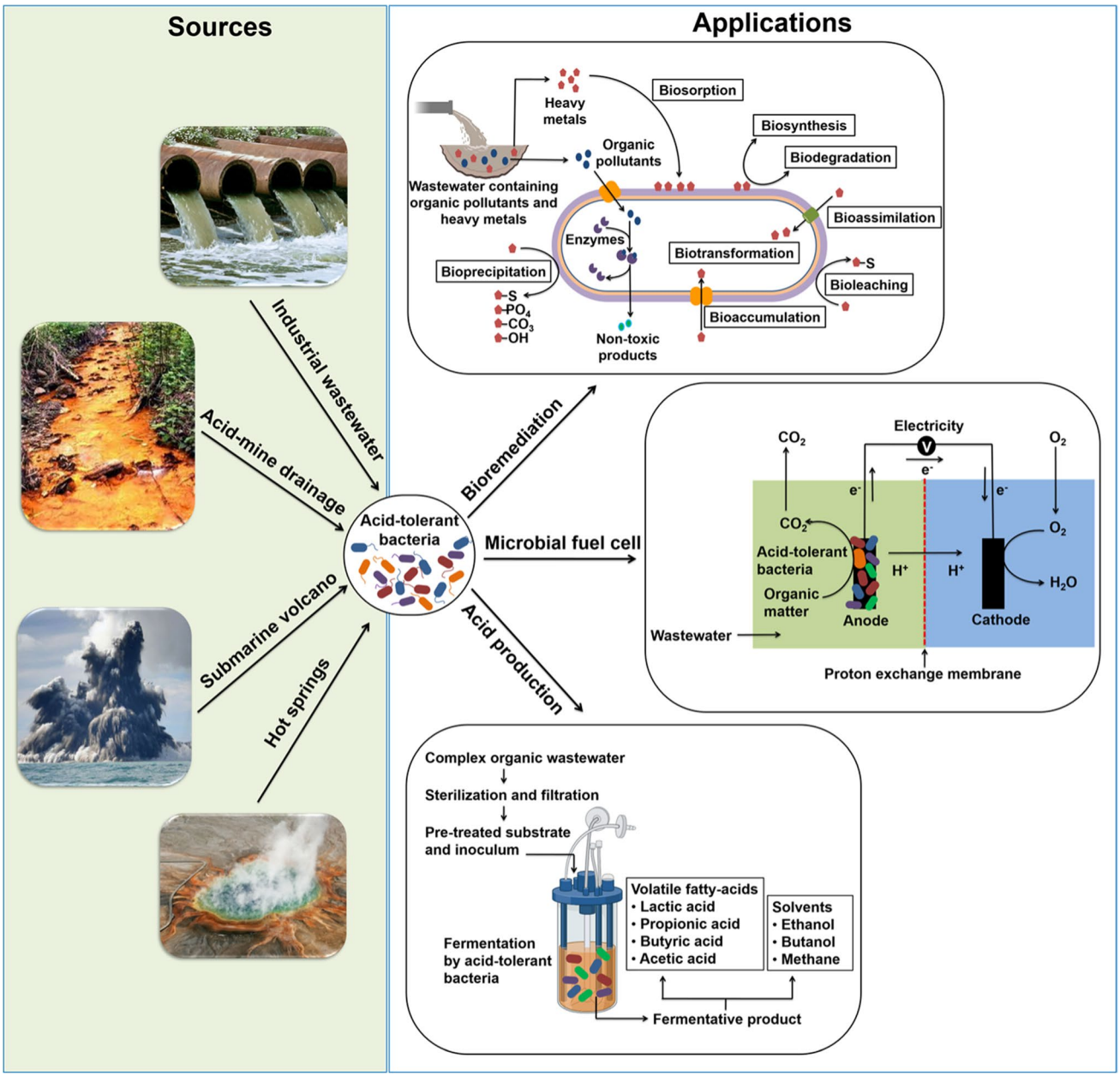

Fig. 5 Schematic representation of the atypical environmental sources of acid-tolerant bacteria and their application in bioremediation, electricity generation, and acid productions

the acidic environment through the process of decarboxylation and deamination. Moreover, the *atpA* gene also helps *Propionibacteria acidipropionici* to sustain the acid stress by the F_1-F_0-ATPase proton pump. The yield of propionic acid can be improved by maintaining pH homeostasis and also by maintaining oxidative potential (Cui et al. 2020). Thus, improving the acid tolerance of *Propionibacteria* can enhance the production of propionic acid.

Acid-tolerant bacteria are widely used in treating wastewater discharged from municipal sewage, agricultural land, and industrial effluents. Apart from wastewater treatment, acid-tolerant bacteria can also generate bio-electricity. A microbial fuel cell (MFC) is a bioelectrochemical device that generates energy as bio-electricity. Acid-tolerant bacteria catalyze the biodegradable compounds present in wastewater and generate bio-electricity. In a microbial fuel cell, acid-tolerant bacteria are placed in the anode chamber which oxidizes the organic and inorganic substrate present in wastewater to generate carbon dioxide, protons, and electrons as the by-product. The protons produced at the anode pass toward the cathode through the proton exchange membrane and the electrons pass to the cathode through an external electrical

circuit. Thus, at the cathode oxygen is reduced. The acid-tolerant bacteria efficiently act as bio-electrocatalysts under acidic conditions, thereby playing a significant role in the microbial fuel cell (Gupta et al. 2021). The member of *Acidithiobacillus* and *Ferroplasma* can produce bioelectricity using tetrathionate as an electron donor from pH 1.5 to pH 3.0 (Ni et al. 2016). However, the power generated from the microbial fuel cell is constrained to high internal resistance. Thus, to increase the amount of electricity produced through microbial metabolic reactions, the system architecture must be greatly improved.

Bioremediation by acid-tolerant strains

Acid-tolerant bacteria are widely used in bioremediation, where bacteria have to survive in acid stress conditions. Bioremediation is the process in which bacteria mineralize or transform harmful organic substances into non-toxic substances, which then take part in natural biogeochemical cycles. Acid mine drainage causes serious environmental hazards. Aluminum, lead, arsenic, and zinc are found in high concentrations in acid mine drainage. Moreover, the high acidity of acid mines further solubilizes the other metals and metalloids thereby increasing the mineral dissolution. The precipitation of metals in wastewater reduces the neutralization capacity and also reduces the pH of the wastewater, causing serious effects on aquatic life. The acid-tolerant bacteria such as *Clostridium* spp. and *Desulfovibrio* spp. remediate the acid mine drainage using an up-flow anaerobic sludge bed reactor (Ayangbenro et al. 2018). *Desulfovibrio* spp. uses F_1–F_0–ATPase proton pump to efflux the intracellular H^+ ions and tolerate the acidic environment.

The wastewater contains a huge amount of organic pollutants and toxic heavy metals (Syam Babu et al. 2020). The microbial bioremediation of the organic pollutants is carried out through enzymatic reactions within the acid-tolerant bacteria, which produce different intermediate metabolites through the metabolic pathways. The metabolizing enzymes such as hydrolases, dehydrogenases, dehalogenases, proteases, and lipases degrade the organic pollutants into non-toxic metabolites which is eco-friendly. The acid-tolerant bacteria can also remediate or detoxify the heavy toxic metals from the wastewater. The bacteria can interact with the heavy metals directly by accumulating the metals on the cell surface through the process of biosorption (Hou et al. 2020). The acid-tolerant bacteria can reduce or oxidize metals and synthesize or degrade metal-containing organic compounds through catalytic reactions through the process of biosynthesis and biodegradation. The metals can assimilate inside the acid-tolerant bacteria through siderophores through the process of bioassimilation (Kuppusamy et al. 2016). The acid-tolerant bacteria can assemble heavy metals in the intracellular space through the protein channel through the process of bioaccumulation. After entering the metals inside the bacterial cell, the inorganic pollutants like arsenic (As^{5+}), chromium (Cr^{6+}), and mercury (Hg^{2+}) are converted to organic As^{3+}, Cr^{3+}, and Hg^0 through the metabolic processes known as biotransformation (Hou et al. 2020). The biofilm-forming acid-tolerant bacteria are more efficient in the removal of metals from the contaminated environment. In addition, biofilm also protects the bacteria from extracellular acid stress. The EPS, the structural integrity of biofilm, protects the bacteria from acid shock and adsorbs the metal cations due to the negatively charged functional groups in their macromolecule structure. The EPS produced by *Desulfovibrio desulfuricans* helps in the biosorption and bioprecipitation of heavy metals like zinc (Zn^{2+}) (Hwang and Jho 2018). Besides, the nanoadsorption of metals was also reported by the acid-tolerant biofilm-forming bacterium *Lysinibacillus sphaericus* RTA-01 which was able to remove Cr^{6+} from the aqueous solution (Kumar et al. 2019).

Sulfate-oxidizing and sulfate-reducing acid-tolerant bacteria are involved in the processes of bioleaching and bioprecipitation respectively (Razia et al. 2023). In biohydrometallurgy, the process of extraction of metals from low grade iron ore and thereby oxidation of toxic metals producing less toxic soluble compounds by the bacteria is known as bioleaching. *Acidithiobacillus ferrooxidans* and *Acidithiobacillus thiooxidans* are acid-tolerant bacteria that help in the process of bioleaching which can oxidize Cr^{6+} to Cr^{3+}. It has been reported that acid-tolerant bacteria including *Clostridium* spp. and *Desulfovibrio* spp. removed high metals and sulfate at an efficiency of 72% (Leiva-Aravena et al. 2019). The consortium of the bacterial species can also rapidly and efficiently remove more heavy metals from the contaminants. It has been reported that the mixed culture of *Desulfovibrio* sp. removed higher concentrations of heavy metals like copper (Cu), cadmium (Cd), and nickel (Ni) than the single strain of *Desulfovibrio vulgaris* (Cabrera et al. 2006). *Pseudomonas aeruginosa* uptakes the metal through metal-chelating agents by producing siderophores which help in the solubility of hydrophobic substances and metal solubility (Saha et al. 2016).

The acid-tolerant bacteria can also be used to bioremediate the wastewater discharged from different industries. *Acidophilus*, *Brevibacterium*, *Halomonoas*, *Leptospirillum*, *Shewanella*, *Stenotrophomonas*, and *Thermogymnomonas*, known as extremely acid-tolerant bacteria can be used for biotreatment of acid mine drainage (Xu et al. 2020). Bacteria help in nutrient removals such as ammonia, phosphate, total nitrogen, nitrite, and nitrate from industrial wastewater. For example, acid-tolerant bacterial strains *Lysinibacillus sphaericus* RTA-01 and *Bacillus pumilus* CTO-05 were reported to remove nitrate and phosphate from the wastewater of the rubber processing industry (Dey et al. 2020). The most conventional technique for the treatment of wastewater is the

addition of alkaline substances to increase the pH of the substrate. Moreover, gene duplications and insertion of acid tolerance genes help the acid-tolerant bacteria for bioremediation (Tian et al. 2019). There are different techniques involved in the remediation. The acid-tolerant bacteria help in the bioremediation of the contaminated sludge inside the bioreactor thereby improving the reproducibility of cultivation conditions, reducing the risk of contamination, etc. (Zhang et al. 2018). After screening the suspended objects, the wastewater passes through the sedimentation tank where the large suspended particulates settled down. The wastewater initially passes through the anoxic tank, thereafter through the aerobic tank where the wastewater is treated with acid-tolerant bacteria (Tanner et al. 2012). The wastewater which is not properly treated is re-circulated to the anoxic tank for re-treatment. From the membrane bioreactor, pure treated water is obtained along with the excess sludge.

Polycyclic aromatic hydrocarbons (PAHs) are usual pollutants present in acidic effluents, like in mine-discharged areas in petroleum-contaminated areas. The biodegradation of PAHs can be productively directed by acid-tolerant bacteria (Rajkumari et al. 2019). *Acidocella* sp. and *Acidiphilium facilis* can degrade the petroleum hydrocarbons, such as toluene, naphthalene phenanthrene, and anthracene at an extremely low pH of 2.0 (Koul et al. 2021). *Pseudomonas putida* can also be used for the biodegradation of petroleum hydrocarbon compounds, such as o-xylene, benzene, and toluene (Miri et al. 2021). Bioremediation by acid-tolerant bacteria is controlled by various factors including temperature, pH, nutrient availability, dissolved gases i.e. oxygen, and various electron acceptors (Liu et al. 2015). Thus, acid-tolerant bacteria use different acid tolerance mechanisms to remove the toxic heavy metals, and various bacterial nutrients such as total nitrogen, phosphate, ammonia, nitrite, and nitrate from the wastewater. The acid-tolerant genes present in the bacteria such as *ybaS*, *cfa*, *dnaK*, and *rpoS* are mainly responsible for the bioremediation and degradation of PAHs. Thus, to enhance the rate of bioremediation and biodegradation the improvement of the acid tolerance gene is of utmost necessity.

Improvement of acid tolerance by engineering acid tolerance gene

Several acid-tolerant genes are engineered for improving acid tolerance through genetic manipulation. There are many genetically engineered strains with acid-tolerant genes for improving acid tolerance as listed in Table 3. The efficient technology for acid tolerance improvement is genome shuffling. Protoplast fusion is also another technology for strain improvement. A mutant library of *Propionibacterium acidipropionici* was prepared by the recombination of the genome using UV irradiation and mutagenesis, followed by protoplast fusion. After several steps of protoplast fusion, acid-tolerant strains are obtained, which successfully enhanced propionic acid production by 65% (Guan and Liu 2020). *Lactococcus lactis* is more resistant to acid stress by expressing glutathione synthetase from *Escherichia coli* and trehalose biosynthetic pathway from *Propionibacterium freudenreichii* (Wu et al. 2014). In *Propionibacterium acidipropionici*, the *atpA* gene is engineered for maintaining intracellular pH by pumping out excess proton by F_1-F_0-ATPase. *Propionibacterium jensenii* ATCC 4868 was engineered with five acid-tolerant genes including *arcA*, *arcC*, *gadB*, *gdh*, and *ybaS* to improve the microbial production of propionic acid (Guan et al. 2016). The *cad* gene is introduced in *Escherichia coli* for the generation of ammonia via deamination and decarboxylation (Noh et al. 2018). The *ybaS* gene is introduced in *Escherichia* coli for protecting against hydrochloric acid (Lu et al. 2013). In *Escherichia coli*, the *cfa* gene is engineered to maintain the fluidity of cell membranes (Kanjee and Houry 2013). *dnaK* is inserted in *Lactococcus lactis* for inducing the expression of heat shock genes (Abdullah-Al-Mahin et al. 2010). The ADAR system controlled the acid tolerance mechanism in *Lactobacillus casei*. Thus, the resistance to acid resistance can be enhanced by the addition of arginine or aspartate, which helps them to sustain the acidic pH of 2.5 for malolactic fermentation.

In *Escherichia coli*, sigma factor, *rpoS* is an optimistic target for enhancing acid-tolerant phenotypes. The up-regulation of noncoding sRNA, *dsrA* coupled with sRNA chaperone, *hfq*, activates the *rpoS*. The activation of *rpoS* increased the acid tolerance in low pH and also increased the survivability upon extreme acid shock. It is observed that the *dsrA-hfq* engineered *E. coli* strain enhances the acid tolerance by 51 to 72% in comparison with the wild strain (Lin et al. 2021). *Pseudomonas putida* can be genetically engineered with the GADR system and regulator, *irrE*. The mutant strain of *Pseudomonas putida* can survive in a hostile environment at low pH, and it can also degrade the benzoate or nicotine with 90% greater efficiency than the wild strain (Zhou et al. 2019). Thus, the mutation of polluting degrading bacteria with the GADR system and *irrE* regulator can successfully remediate the acidic wastes.

The accession of the acid-tolerant genes in bacteria develops additional acid tolerance mechanisms. Further, genetically engineered bacteria help in bioremediation and biodegradation. Thus, the role of acid tolerance genes in various physiological conditions might be investigated for further development of the techniques of bioremediation. However, the implication of advanced genetic engineering approaches and further characterization of acid-tolerant genes are required for efficient, and viable bioremediation of industrial wastewater, heavy metals, and biodegradation of organic pollutants.

Table 3 Application of genetically engineered strain with acid-tolerant genes for improving acid tolerance

Acid-tolerant genes	Acid-tolerant bacteria	Acid stress	Function	Reference
ybaS	*Escherichia coli*	Hydrochloric acid	Consumption of intracellular H^+ ions.	Lu et al. 2013
ybaS	*Propionibacterium acidipropionici*	Propionic acid	Production of NH_3 via deamination and decarboxylation.	Guan and Liu 2020
arcA	*Propionibacterium acidipropionici*	Propionic acid	Consumption of intracellular H^+ ions	Guan and Liu 2020
gadB	*Propionibacterium acidipropionici*	Propionic acid	Production of NH_3 via deamination and decarboxylation.	Guan and Liu 2020
gadC	*Escherichia coli*	Hydrochloric acid	Production of NH_3 via deamination and decarboxylation.	Lu et al. 2013
Cad	*Escherichia coli*	Acetic acid	Consumption of intracellular H^+ ions.	Noh et al. 2018
atpA	*Propionibacterium acidipropionici*	Propionic acid	Pumping proton out of the cell via F_1–F_0 –ATPase proton pump.	Guan and Liu 2020
cgAMDl	*Candida glabrata*	Hydrochloric acid	Pumping proton out of the cell via F_1–F_0 –ATPase proton pump.	Wu et al. 2018
dnaK	*Lactococcus lactis*	Lactic acid	Induce the expression of heat shock genes in the response to protein misfolding.	Abdullah-Al-Mahin et al. 2010
recA	*Helicobacter pylori*	Lactic acid	Activation of SOS response.	Adikesavan et al. 2011
uvrA	*Streptococcus mutans*	Acetic acid	Repair DNA damage by nucleotide-excision repair.	Zheng et al. 2018
PEP3	*Acetobacter aceti*	Acetic acid	Protecting the organelle from acid stress.	Ding et al. 2015
FPSl	*Acetobacter aceti*	Acetic acid	Modulating the integrity, lipid composition, and fluidity of cell membranes.	Zhang et al. 2011
rpoS (dsrA, hfq)	*Escherichia coli*	Organic acid	Increased the acid tolerance in low pH, increased the survivability upon extreme acid shock, and enhance the acid tolerance rate.	Lin et al. 2021
GDAR system, *ire*	*Pseudomonas putida*	Benzoic acid	Degrade the benzoate or nicotine with 90% greater efficiency.	Zhou et al. 2019

Conclusion

The acid-tolerant bacteria have developed several distinct cellular and genetic mechanisms to sustain the acidic stresses. The acid-tolerant bacteria can tolerate the low pH for several hours due to the expression of acid tolerance mechanisms. There are different mechanisms of acid tolerance efficiently work together for the survival and proper metabolism of the bacteria in an acidic stress environment. Among various acid tolerance mechanisms, the most common cellular mechanisms are activation of the F_1–F_0–ATPase proton pump, production of alkali compounds, increasing the urease activity, biofilm formation, and protection or repairing of macromolecules. Several acid-tolerant genes also help the acid-tolerant bacteria to tolerate the acidic environment. Some acid-tolerant bacteria employ more than one tolerance mechanism for maintaining pH homeostasis. However, acid-tolerant bacteria can also alter the membrane bioenergetics and membrane fluidity for survival in hostile conditions. These acid-tolerant components are used in various aspects like in industrial bioprocesses and the treatment of industrial effluents. Bacteria-mediated bioremediation is advantageous as these are eco-friendly, feasible, and low-cost efficient methods of degrading harmful toxic compounds. The development of novel genetically engineered strains with acid-tolerant genes may improve the efficiency of the transgenic acid-tolerant bacteria towards the treatment of industrial effluents as well as the synthesis of various industrial bioprocesses.

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Declarations

Ethics approval This paper does not contain any studies with human participants or vertebrate animals performed by any of the authors.

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