Brazilian Journal of Microbiology (2021) 52:1701–1718
https://doi.org/10.1007/s42770-021-00624-x

BACTERIAL AND FUNGAL PATHOGENESIS - REVIEW

Microbial biofilm: formation, architecture, antibiotic resistance, and control strategies

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Received: 16 October 2020 / Accepted: 19 September 2021 / Published online: 23 September 2021

Abstract

The assembly of microorganisms over a surface and their ability to develop resistance against available antibiotics are major concerns of interest. To survive against harsh environmental conditions including known antibiotics, the microorganisms form a unique structure, referred to as biofilm. The mechanism of biofilm formation is triggered and regulated by quorum sensing, hostile environmental conditions, nutrient availability, hydrodynamic conditions, cell-to-cell communication, signaling cascades, and secondary messengers. Antibiotic resistance, escape of microbes from the body's immune system, recalcitrant infections, biofilm-associated deaths, and food spoilage are some of the problems associated with microbial biofilms which pose a threat to humans, veterinary, and food processing sectors. In this review, we focus in detail on biofilm formation, its architecture, composition, genes and signaling cascades involved, and multifold antibiotic resistance exhibited by microorganisms dwelling within biofilms. We also highlight different physical, chemical, and biological biofilm control strategies including those based on plant products. So, this review aims at providing researchers the knowledge regarding recent advances on the mechanisms involved in biofilm formation at the molecular level as well as the emergent method used to get rid of antibiotic-resistant and life-threatening biofilms.

Keywords Biofilm · Quorum sensing · Antibiotic resistance · Plant · Biofilm formation · Antibiofilm

Introduction

Microorganisms can live in free form or in a consortium of different or same species, called biofilm. Biofilms are an ordered and arranged group of microorganisms living within an extracellular polymeric substance (EPS) matrix produced by them and are adhered to each other on living or non-living surfaces and show variations in terms of growth rate and gene expression when compared to their planktonic form [1–3]. To develop a relationship with the host, to show resistance towards hostile external conditions, and to cope with the known antibiotics and other environmental cues, the microorganisms have evolved to form a protective cover around themselves [4]. Biofilm formation contributes towards the development of antibiotic resistance and the formation of persistent cells which are responsible for the unmanageable persistence of microbial infections [5]. Biofilms have various pathological manifestations and exist almost everywhere, inhabiting medical implants, living tissues, water channels, pipes, hospital floors, food processing units, and other biotic and abiotic surfaces [6, 7]. Changes in phenotype and gene expressions accompanied by the resistance to known antibiotics, metabolic activity and growth rate reduction, and production of virulence-associated factors are some features of biofilm-associated microorganisms [1, 8]. As per the reports of the National Institutes of Health (NIH), about 65% and 80% of microbial and chronic infections, respectively, are caused by microbial

Responsible Editor: Carla Taddei

Highlights
- Biofilm is a safe and antibiotic-resistant home to microorganisms.
- Biofilm formation is a complex and quorum sensing–dependent process.
- Polysaccharides, proteins, eDNA, etc. are the architecture and stability determinants of biofilm.
- Recent advances in physical, chemical, and biological antibiofilm strategies.

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biofilms, infecting both tissues and medically implanted devices. Breast implants, ventricular shunts, tissue fillers, ventricular-assisted devices, contact lenses, catheters, joint prostheses, urinary catheters, orthopedic implants, pacemakers, mechanical heart valves, defibrillator, vascular grafts, endotracheal tubes, voice prostheses, etc. are some examples of medically implanted devices often infected by microbial biofilms [2]. Some of the tissue-related infections caused by microbial biofilms include periodontitis, osteomyelitis, lung infection in cystic fibrosis, endocarditis, dental plaque, chronic tonsillitis, chronic laryngitis, chronic wounds, and biliary and urinary tract infections [9]. As per the reports of the Centers for Disease Control, 2007, there were about 1.7 million hospital-acquired infections, more than 0.5 million associated deaths, and an economic burden of about US$11,000 million to cure biofilm-associated infections [10]. Furthermore, different sectors of the food industry, viz. poultry, dairy, ready-to-eat, aquaculture, etc., are severely affected by biofilm-producing microorganisms resulting in food spoilage, disease outbreaks, and deaths [11]. So, keeping in view the prevalence of biofilm-associated microorganisms and inefficiency of current antibiotics, the situation requires a transition towards the formation of non-toxic and potent antibiofilm agents targeting signaling pathways regulating quorum sensing (QS), EPS synthesis, biofilm-related genes, microbial motility, adhesion, dispersion, and many more [12–14]. The recent novel antibiofilm approaches include the use of ultrashort antimicrobial peptide nanoparticles [15], host defense peptides (HDPs) [16], surface-active organosilane biocide-Goldshield (GS5) [17], biofilm-specific peptides [18], smart antibiofilm surfaces [19], nanoelements (NEs) [20], and poly(ether urethane) (PEU) films for disposal of antibiofilm agents like gallium (Ga) or zinc (Zn) [21].

Biofilm formation: surface colonization

Biofilm formation is a multi-step and complex process that involves the transition of bacteria from free-swimming planktonic form to biofilm-making sessile form. The whole process of formation is influenced by external conditions like temperature, pH, gravitational forces, hydrodynamic forces, Brownian movements, nature of the inhabiting surfaces, quorum sensing, secondary messengers, and other signaling molecules as well [2, 22]. As shown in Fig. 1, different stages of biofilm formation can be divided into four major steps [23].

Attachment: a surface-sensing step

The process of biofilm formation is triggered with the adherence of planktonic microorganisms to surfaces and, thus, considered as an important stage to develop the free-flowing microorganisms into an assembled community structure [24]. During the initial stage of biofilm formation, microorganisms are loosely and reversibly attached to surfaces and this stage is characterized by the presence of polarly attached microorganisms to the surfaces. Thereafter, microorganisms change the orientation to lay flat on the surfaces and go for irreversible attachment which develops resistance to many physical factors hindering biofilm formation [25]. Bis-(3′-5′)-cyclic dimeric guanosine monophosphate (c-di-GMP) is an intracellular signaling molecule that plays a vital role in early events of biofilm formation by restricting flagella-mediated swimming motility and increasing biofilm matrix production [26]. The c-di-GMP concentration increases with each attachment/detachment event due to Pil-Chp surface–sensing system present on microbial surfaces. So,

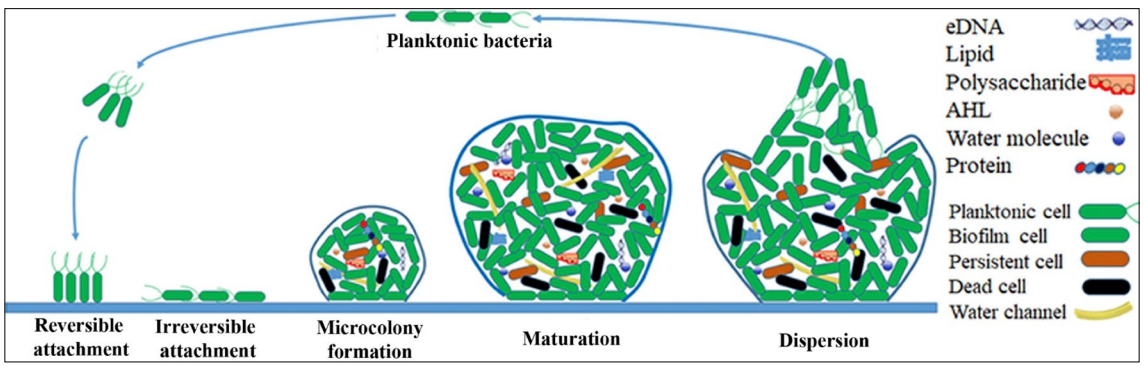

Fig. 1 Steps of biofilm formation. The multi-step biofilm formation starts with the attachment of planktonic microorganisms to the surfaces which is sub-divided into reversible and irreversible attachment followed by microbial division to form microcolonies. Microcolonies undergo maturation characterized by specific composition, shape, and architecture followed by dispersion of biofilm to repeat the cycle. A mature biofilm is a heterogeneous mixture of planktonic (green flagellated), sessile (green), persistent (brown), dead (black) cells, water channels, and different types of signaling and stabilizing molecules like acyl-homoserine lactones (AHL), lipids, polysaccharides, proteins, extracellular DNA (eDNA)

early events of biofilm formation involve the conversion of surface naïve planktonic cells (bacteria that exhibit low concentration of c-di-GMP and have not encountered surfaces initially) to surface sentient planktonic cells (bacteria that exhibit a high concentration of c-di-GMP and have encountered surfaces initially) and irreversible attachment of cells to surfaces leading to biofilm formation [27].

Growth or microcolony formation

Soon after the successful adhesion of microorganisms to the surfaces, the adhered microorganisms start multiplication and aggregation within self-produced EPS leading to the microcolony formation in presence of a high concentration of c-di-GMP. Flagella and type IV pili-mediated motilities are important for interactions between microorganisms and surfaces, and cell–cell aggregations to form microcolonies, respectively [28].

Maturation

EPS plays a crucial role in biofilm maturation as it helps in microbial attachment to surfaces, stabilizing the 3-D structure of the biofilm, grouping cells together, protecting from various stresses like host immune system response, antimicrobials, oxidative damage, and metallic cations, and also encapsulating signaling molecules required for quorum sensing, metabolic products, and enzymes [29]. A mature biofilm may acquire a "mushroom" or "tower" shape structure in which microorganisms are arranged as per aero-tolerance and metabolism rate [28]. Otto [30] demonstrated the role of surfactants and modulins in *Staphylococcal* biofilm maturation through quorum sensing–mediated mechanisms. A mature biofilm is a three-layered structure: inner regulating layer, middle microbial basement layer, and outer layer inhabited by the planktonic form of microorganisms that are ready to exit the biofilm [22].

Dispersion

Finally, matured biofilm ruptures actively (motility and EPS degradation–dependent dispersion) or passively (physical factors like liquid flow-dependent dispersion) to disperse the microorganisms to start a new cycle of biofilm formation. Some factors which are mainly responsible for the dispersion of matured biofilm include outgrown population, intense competition, lack of nutrients [28], enzyme action that causes alginate digestion in *Pseudomonas* spp. [31], and variation in environmental conditions like temperature, oxygen deficiency, and metabolite accumulation as well as upregulation of genes responsible for cell motility and EPS degradation, and downregulation of genes important for polysaccharide and fimbriae synthesis [32].

Composition of biofilm: an amalgam of complexity, heterogeneity, and variability

Biofilm is a heterogeneous structure comprising mainly of microbial cells (10–25%) and self-produced EPS matrix (75–90%) as shown in Table 1 [33]. Furthermore, in a heterogeneous biofilm, the interstitial voids or water channels of biofilm are required to separate microcolonies from each other [34]. EPS forms a scaffold that holds the biofilm together and, thus, helps in cell-to-cell communication and provides adhesion and cohesion forces required for biofilm formation. EPS helps in nutrient cycling, maintaining the availability of deoxyribonucleic acid (DNA) for horizontal gene transfer (HGT), and acts as a protective barrier against oxidizing biocides, antibiotics, ultraviolet radiations, desiccation, and host immune defense system [35].

The main constituents of EPS could be categorized as follows.

Polysaccharides

Most of the polysaccharides are heterogeneous while some are homogeneous as well like cellulose, sucrose-derived fructans, and glucans [36]. Various interactions like van der Waals interactions, electrostatic attractive and repulsive forces, ionic attractive forces, and hydrogen bonds promote interaction of polysaccharides with themselves or with proteins and ions required for maintaining structure and stability of biofilm matrix [37]. In *Pseudomonas aeruginosa*, three exopolysaccharides, namely Pel, Psl, and alginate, contribute predominantly to biofilm formation and maintaining biofilm architecture [38]. The role of the polysaccharides is to act as a molecular glue required for bacterial adhesion to each other and to biotic and abiotic surfaces for colonization besides playing a protective role against the immune system, and other external stresses [39].

Extracellular proteins

Extracellular proteins in the biofilm matrix are the amalgam of secreted extracellular proteins, protein subunits of

Table 1 Composition of biofilm

S. no	Components	Percentage (%)
1	Microbial cells	2–5
2	Water	Up to 97
3	Polysaccharides	1–2
4	Proteins	< 1–2 (including enzymes)
5	DNA and RNA	< 1–2

cell appendages such as pili and flagella, cell surface adhesions, and outer membrane vesicle proteins. They interact with exopolysaccharides and nucleic acid components, thus help in biofilm matrix stabilization, surface colonization, and maintaining integrity and architecture of biofilm [40]. Some proteins help in biofilm matrix degradation and dispersal like proteases that dissolve matrix proteins [41], glycosyl hydrolase dispersin B that degrade polysaccharides [42], and DNases that break extracellular nucleic acids [43, 44]. Jiao et al. [45] reported a significant difference between the proteome composition of EPS and that of individual cell fraction and found a pronounced concentration of protein peptidases, cell wall, and polysaccharide metabolism enzymes, disulfide-isomerases, and chaperones like cold shock and DNA binding proteins in EPS matrix. Toyofuku et al. [46] demonstrated that about 30% of EPS matrix proteins were membrane proteins which were found in outer membrane vesicles (OMVs) while some portion of proteins were derived from lysed cells and secreted proteins in *P. aeruginosa.*

Extracellular DNA

Extracellular DNA (eDNA) is one of the key constituents of the EPS matrix which is important for microbial aggregation within a biofilm. The mechanism of origin of eDNA is diverse as it is released through bacterial secretion systems, cell death because of phages, autolysis, quorum sensing–regulated DNA release, or maybe found in association with DNA-containing OMVs [47–51]. In the case of human infections like cystic fibrosis (CF), the eDNA in *P. aeruginosa* is derived from human polymorphonuclear leukocytes (PMNs) which approach the site to fight against infection [52]. eDNA guides motility, provides structural stability, and chelates pathogenicity and antibiotic resistance enhancing cations [53–55]. eDNA also plays a comprehensive role in cell adhesion, maintaining matrix structural integrity, HGT, and protection from host immune system and antibiotics [56]. Wilton et al. [50] reported that eDNA is responsible for matrix acidification which contributes towards increased resistance of *P. aeruginosa* against antibiotics. Also, Harmsen et al. [57] found the role of eDNA in attachment and biofilm formation in *Listeria monocytogenes* strains.

Surfactants and lipids

Some species like *Rhodococcus* spp. produce hydrophobic EPS and adhere to Teflon and colonize waxy surfaces [58]. Ron and Rosenberg [59] reported the role of biosurfactants in the binding of heavy metals and the production of virulence factors. Some lipids with surface-active properties available in the EPS matrix are surfactin, emulsan, and viscosin. They increase the availability of hydrophobic substances by dispersing them out [36]. Rhamnolipids, an important class of surfactants studied in *P. aeruginosa*, initiate microcolony formation, help in shaping biofilm, and facilitate biofilm dispersion as well [60, 61].

Water

Water is regarded as the largest component of the EPS matrix of biofilm. It keeps the biofilm hydrated and protects it from desiccation even during environmental water content fluctuations [36]. The flow and maintenance of essential nutrients within a biofilm are attributed to the amount of water available [62].

Architecture of biofilm: the structural and stabilizing parameter of biofilm

The antibiotic resistance and other functional features of a biofilm are related to biofilm structure, the shape of a matrix, and the 3-D arrangement of microorganisms [63]. The heterogeneous local environmental conditions within biofilm influence gene expression and other metabolic activities of biofilm-forming cells [64, 65]. The water channels and poreless highly packed cells are the two main components of biofilm architecture [66]. The structural knowledge about biofilms is of greater importance to know about the survival and behavioral strategies of biofilms. Bridier et al. [64] monitored the variability of biofilm structure and formation by analyzing some specific biofilm parameters, viz. substratum coverage, bio-volume, roughness, and thickness, and found significant intra- and inter-species variability. By using confocal laser scanning microscopy (CLSM), they found a marked difference in biofilm structures in terms of dispersion, roughness, and aggregation and analyzed that *Escherichia coli* and *L. monocytogenes* strains formed rough biofilms with variable thickness, while *Salmonella enterica* produced small scattered cell clusters. Also, *Staphylococcus aureus* strains show variability in the structure of biofilms as some produced flat and densely packed structures while others formed scattered ones. Similarly, *P. aeruginosa* and *Enterococcus faecalis* formed mushroom-shaped, and flat and compact biofilms, respectively, suggesting that the biofilm architecture differs from microbe to microbe. Environmental factors, cell-to-cell communication, and secondary messengers like cAMP and c-di-GMP shape biofilms to provide microorganisms better adaptability to the local environment [29]. Some other important factors which influence the biofilm architecture are nutrient abundance, hydrodynamic conditions, bacterial motility, cationic and anionic concentration, and availability of proteins and exopolysaccharides within a biofilm. The exopolysaccharides in *E. coli* [67] and *Vibrio cholerae* [68] help in three-dimensional biofilm

formation. Alginate, a well-studied exopolysaccharide in *P. aeruginosa*, helps in forming and maintaining biofilm architecture [69]. The secreted protein TasA and exopolysaccharide in *Bacillus subtilis* biofilm matrix are important for forming fruiting-body-like biofilm and maintenance of matrix integrity [70]. Biofilm architecture is also altered by acetyl groups, the common substituents of exopolysaccharides, as they are believed to be responsible for increased adhesive and cohesive properties of biofilm [36].

Proteins involved in maintaining architecture and stability of biofilm

McCourt et al. [71] described the role of surface binding fibronectin-binding proteins FnBPA and FnBPB in biofilm formation of the methicillin-resistant *S. aureus* (MRSA) strain LAC. They found that both FnBPA and FnBPB help in bacterial aggregation, thus assist in the initial attachment of bacteria on the surfaces. Liang et al. [72] carried out a study on the new cell surface protein BapA1 which is important for adhesion and biofilm formation through BapA1-mediated cell–cell interactions. It contains nine putative pilin isopeptide linker domains required for aggregation of pilus in various Gram-positive bacteria like *Streptococcus parasanguinis*. They reported that the mutant generated by deletion of 3′ portion of the *bapA1* gene lacks a cell wall–sorting signal important for cell surface fibril formation, thereby inhibiting biofilm formation and autoaggregation of bacteria. Eukaryotic microorganisms like fungi also have been reported to form a biofilm to resist environmental ques. Manfiolli et al. [73] reported that mutants of mitogen-activated protein kinase (MAPK) (MpkA, MpkC, and SakA) decrease the adherence of *Aspergillus fumigatus* to plates in in vitro conditions. They also analyzed the impact of *A. fumigatus* protein phosphatase PphA on biofilm formation and found that *ΔpphA* strain cell wall has less chitin, more β-(1, 3)-glycans, more susceptible to cell wall-damaging agents, less adhesion, and biofilm formation. *Streptococcus mutans* is responsible for dental caries as it forms a biofilm in the form of dental plaque. *S. mutans* secrete *comCDE* code peptide signal molecule called a competence-stimulating peptide (CSP) that senses cell density and environmental stresses that directly influence biofilm formation [74]. Ye et al. [75] reported the role of outer membrane protein W (OmpW) in biofilm formation along with survivability of *Cronobacter sakazakii* under salt stress conditions and found that both survival rates and biofilm formation increase with the synthesis of OmpW. Polysaccharide intercellular adhesin (PIA) involved in bacterial cell attachment is replaced by protein components in several virulent *S. aureus* strains. The *suhB* gene is important for the production of extracellular amyloid fibers. Overexpression of staphylococcal SuhB (SaSuhB) in *E. coli* produces extracellular macroscopic fibers made of recombinant SaSuhB protein which helps in cell adhesion as the fibers are sticky [76]. Arenas and Tommassen [77] discussed the adhesion of *Neisseria meningitidis* through a complex network of eDNA and positively charged surface-exposed proteins. Similarly, Bandekar et al. [78] discussed the role of chromosome I encoded VC0395_0300 protein (Sebox3) of *V. cholerae* in biofilm formation by synthesizing c-di-GMP from guanosine-5′-triphosphate (GTP). Gordonii surface protein B (GspB) in *Streptococcus gordonii* [79], accessory Sec system SecY2A2 (serine-rich repeat surface protein, PsrP) in *Streptococcus pneumoniae* [80], and phosphoenolpyruvate phosphotransferase system (PTS) in *Klebsiella pneumoniae* [81] play important roles in biofilm formation by enhancing bacterial aggregation, substrate binding, and extracellular matrix production, respectively. These examples give an insight that the expression of different proteins plays an important role in stabilizing and maintaining the architecture of biofilm.

Signaling cascades and genes involved in biofilm formation

Extracellular quorum sensing and intracellular cyclic dinucleotide signaling cascades are important in biofilm formation. It has been found that the two cascades may converge and regulate each other during biofilm formation, thus enhance biofilm formation synergistically [82]. Quorum sensing is the intercellular communication that senses cellular density through signaling molecules like N-acyl-homoserine lactones (AHL), the autoinducing peptide (AIP), and autoinducer-2 (AI-2) in Gram-negative, Gram-positive, and both, respectively, and plays a vital role in biofilm formation [83]. Four QS systems are reported in *P. aeruginosa*, viz. *las*, *rhl*, PQS, and integrated QS (IQS). They follow the hierarchical order; thus, these cascades regulate each other through QS-related genes and other transcription factors [84]. c-di-GMP could regulate quorum sensing by affecting the expression of autoinducer synthases; likewise, quorum sensing regulates the level of c-di-GMP by influencing genes encoding proteins having phosphodiesterases A (PDEA) and diguanylate cyclase (DGC) activities in *Thermotoga maritima* [85]. Li et al. [86] discussed the importance of glycolysis and gluconeogenesis in biofilm formation as they concluded that glycolysis pathway genes were downregulated and gluconeogenesis genes were upregulated during attachment while glycolysis pathway genes were upregulated and gluconeogenesis genes were downregulated during the maturation period of biofilm formation. They also discussed the involvement of cAMP-PKA and MAPK signaling pathways and *Mga1*, *Phd1*, *Sok2*, and *Ash1* genes in the biofilm formation of *Saccharomyces cerevisiae*. In another study,

it was demonstrated that mutation in PA0240-encoding putative porin proteins, PA3710-encoding putative alcohol dehydrogenase, and PA3782-encoding putative AraC-like transcriptional regulator downregulates biofilm development of *P. aeruginosa* as analyzed through in vivo expression technology system (IVET) [87]. Manfiolli et al. [73] studied signal transduction pathways necessary for adhesion and biofilm formation of *A. fumigatus* suggesting that MAP kinases like SakA, MpkA, and MpkC play a significant role in biofilm formation by enhancing the adhesion and extracellular matrix (ECM) production. Furthermore, phosphatase null mutants, Δ*ptcB* and Δ*sitA*, were found to degrade cell wall, thus concluded that phosphatases maintain cellular integrity and regulate phosphorylation of MpkA and SakA. Generally, initial microbial adherence and multiplication within the host depend on host environmental signals/factors like pH, temperature, insulin, steroid hormones, monoamines, and vitamin K that mimic and act as exogenous quorum signaling compounds [88]. Horng et al. [81] demonstrated the role of phosphoenolpyruvate and PTS on enhancing biofilm formation in *K. pneumoniae*. They found an enzyme II complex, a homolog of PTS: KPN00353–KPN00352–KPN00351, and reported that expression of *KPN00353–KPN00352–KPN00351* genes releases putative enzyme II complex in PTS that increases synthesis of capsular polysaccharide and eDNA necessary for biofilm formation. *ARO1* gene of *Candida albicans* is important for the production of a multifunctional enzyme which in turn is required for the synthesis of aromatic amino acids through the shikimate pathway. *ARO1* gene knockdown effects on biofilm formation in *C. albicans* were studied by Yeh et al. [89] and it was found that it is involved in cell wall biogenesis and maintaining integrity through activation of Mkc1 signaling cascade. Chambers and Sauer [90] discussed the role of small non-coding RNAs (sRNAs) like ArcZ targeting CsgD in *E. coli* and *Salmonella typhimurium* [91], RsmY and RsmZ targeting RsmA in *P. aeruginosa* [92], and Qrr1–4 targeting AphA in *V. cholerae* [93] in biofilm formation in response to environmental factors by regulating the transition of planktonic to sessile form. In a polymicrobial association of *A. fumigatus* and *P. aeruginosa*, Zheng et al. [94] discussed the transition in *A. fumigatus* from vegetative growth to conidiation by phenazine-derived metabolites synthesized by *P. aeruginosa* through NapA oxidative stress signaling cascade. Autoinducer-2 (AI-2) upregulates quorum sensing in *Staphylococcus epidermidis* by enhancing transcription levels of *ica* operon and *bhp* (a biofilm-associated protein along with *icaR*). Thus, AI-2 enhances quorum sensing and biofilm formation through *ica*- and bhp-dependent mechanisms [95]. Wotanis et al. [96] discussed the major role of the NspS/MbaA signaling complex in *V. cholerae* biofilm formation. Polyamines secreted by Vibrionales as environmental signaling molecules regulate biofilm formation in *V. cholera* positively. NspS/MbaA signaling cascade detects extracellular polyamine norspermidine which binds to NspS periplasmic binding protein, restricts MbaA's phosphodiesterase activity, and increases levels of second messenger c-di-GMP which is known to enhance biofilm formation.

Antibiotic resistance of biofilm: an adaptive and strategic success of microorganisms

The increase of antibiotic resistance of microorganisms throughout the world is a worrying matter for humans, veterinary, food, and other sectors [97]. Biofilms are resistant to antibiotics and disinfectants and impervious to phagocytosis, and tolerate the body's immune system mainly because of self-produced EPS [98]. A multi-layer defense system is constituted in biofilm by the formation of persister cells, development of adaptive stress responses, very less antibiotic penetration, limited nutrition, less growth and metabolic activity [99], and inactivation of antimicrobials within the components of the EPS matrix [100]. Ju et al. [101] reported about a 32,768 times increase in antibiotic resistance in the biofilm phenotype *Salmonella* serovar Dublin as compared to their planktonic form. Hu et al. [102] demonstrated biofilm formation and subsequent increased antibiotic resistance of foodborne *Clostridium perfringens.* Guo et al. [103] compared the abundance of antibiotic-resistant genes (ARGs) in naturally occurring biofilms in comparison to associated sediment and water samples and detected a high frequency of ARGs, viz. *sul*1, *sul*2, *tet*A, and *tet*W, in biofilms as compared to sediment and water samples. Aslantaş and Demir [104] studied biofilm formation and antibiotic resistance of *S. aureus* isolates from subclinical bovine mastitis cases and reported overexpression of adhesion and biofilm-related genes along with resistance to β-lactam antibiotics. The factors which contribute towards antibiotic resistance of biofilm include restricted antimicrobial penetration, antibiotic-modifying enzymes in matrix, eDNA, hypoxia, reduced growth, variability in physiology, oxidative stress and amino acid starvation responses, efflux pumps, quorum sensing, persister cells, HGT, high mutation rate, and colony variants [100]. Some factors are discussed in detail in the next section.

Low metabolic activity, slow growth, and antibiotic resistance

It has been reported that there is an oxygen gradient within a biofilm. The concentration of oxygen near the surface of biofilm is highest and declines towards the center, creating almost anaerobic conditions in the center [105]. Totani et al. [106] reported that low oxygen condition promotes

while normoxia hinders biofilm formation. There is a similar stratification in metabolic activity, growth, and protein synthesis in biofilms with a high rate at the surface and no or very less rate in the center resulting in less penetration and consumption of antibiotics in the biofilm [107]. The phenotypic diversity of microorganisms within biofilm due to depleted nutrients, oxygen, and other responses promotes asynchronous growth and differential gene expression that leads to drug tolerance through regulation of genes important for DNA repair, lipid biosynthesis, toxin efflux, and ion sequestration [9, 108].

Impact of horizontal gene transfer on resistance development

Biofilm acts as a reservoir of antibiotic resistance genes (ARGs, the resistome) which are found to be responsible for providing antibiotic resistance to pathogens through HGT [109] conjugation [110, 111], transformation [112], and transduction [113, 114]. HGT acclimates bacteria to the changing environment and favors biofilm formation and resistance to antibiotics [115]. HGT gives rise to new variants without inducing mutation in the variant [116]. Fan et al. [117] discussed that HGT maintains structural stability, integrity, and robustness of microbial communities coexisting together. HGT contributes towards several traits including pathogenicity and antibiotic resistance in *E. faecalis* responsible for persistent endodontic infection [118].

Persister cells and antibiotic resistance

Biofilms are characterized by the presence of persister cells—a specialized phenotype of bacterial cells that neither grow normally nor die even in the presence of potent antibiotics. Persister cells are regarded as dormant variants of regular cells [119]. Persister cells within the biofilm can survive the high dose of antibiotic treatment as well as the immune defense system. But upon reduction of the antibiotics, persister cells can repopulate in the biofilm [120]. Persister cells are genetically similar but physiologically different from parent cells. They are formed under environmental stress conditions within the biofilm and show special characteristics, viz. they are metabolically inert, show slow growth and replication, regulate the toxin-antitoxin system, show ineffectiveness towards antibiotics, upregulate phosphate metabolism, and enhance anti-oxidative and DNA repair system [121]. Antibiotics kill planktonic cells and some proportion of biofilm cells, decreasing their population, but show ineffectiveness towards the persister cells. As a result, antibiotic-resistant persister cells reproduce, disperse out of biofilms, and form new biofilms [122].

Role of eDNA in antibiotic resistance

Colonization of bacteria on surfaces releases proteins, exopolysaccharides, and eDNA which confer stability and structural integrity and promote proper nutrient distribution to the forming biofilm [123]. eDNA is produced by cell lysis and active secretions and has been reported to promote microbial adhesion, inhibit antimicrobial diffusion, and chelate cations [56] besides suppressing innate immune response [124]. It has been reported that eDNA contributes to cation gradients, genomic DNA release, and inducible antibiotic resistance. Mulcahy et al. [125] demonstrated the induction of eDNA-mediated antibiotic resistance in *P. aeruginosa* biofilm by regulating PhoPQ and PmrAB cationic antimicrobial peptide resistance operon *PA3552–PA3559* system. One of the reported mechanisms is that eDNA attaches and chelates positively charged aminoglycosides and antimicrobial peptides as proved by Chiang et al. [126] in *P. aeruginosa* biofilms. Jakubovics and Burgess [127] discussed the role of eDNA in the promotion of bacterial adhesion, maintaining structural integrity, the evolution of bacteria through genetic recombination and HGT, shielding against antimicrobials, and serving as a source of phosphorous.

Efflux pumps and antibiotic resistance

Efflux pumps are proteinaceous active transporters embedded within cytoplasmic membranes. The resistance-nodulation-division family (RND), the multidrug and toxic compound extrusion family (MATE), the small multidrug resistance family (SMR), the major facilitator superfamily (MF), and the ATP-binding cassette family (ABC) are different classes of efflux pumps reported in bacteria by Kumar and Schweizer [128] and Singh et al. [129]. Efflux pumps induce antibiotic resistance to microorganisms by pushing intracellular toxins including antibiotics away from intracellular targets back into extracellular space [100]. Although efflux pumps are active in planktonic bacteria as well, they are upregulated in biofilms leading to multidrug resistance (MDR) [28, 129]. Several efflux pump genes and their overexpression in the biofilm have been reported like efflux pump gene PA1874–1877 in *P. aeruginosa* [130]; the overexpressed RND efflux pumps like BCAL1672-1676 (RND-3) provide biofilm resistance against tobramycin and ciprofloxacin while BCAM0925-0927 (RND-8) and BCAM1945-1947 (RND-9) protect biofilms from tobramycin in *Burkholderia cepacia* [131].

Role of antibiotic-modifying enzymes of matrix on resistance development

Another important mechanism for antibiotic resistance is an enzymatic modification of antibiotics to a non-toxic form

within EPS. Such enzymes enhance virulence and induce resistance against antibiotics, thus regarded as exotoxins. Lyases, group transferases, hydrolases, and redox enzymes are the reported classes of antibiotic-modifying enzymes [132]. They modify and, thus, inactivate antibiotics by either cleaving chemical bonds necessary for the functioning of enzymes or restricting the binding of antibiotics to specific targets [133]. β-Lactamase secreted by *K. pneumoniae* biofilms destroys ampicillin and inhibits it from targeting cells [134]. In infected cystic fibrosis lung, over-synthesis of AmpC cephalosporinase has a specific role in providing antibiotic resistance to *P. aeruginosa* [135].

Escape of biofilm cells from immune system: an evading success

An immediate response is established in the body through immune cells, receptors, and several humoral factors like mannose-binding lectins, and antibodies of innate immunity upon infection [136]. Microbial biofilms are reported to escape the body's immune system. *S. aureus* biofilms may evade host immunity by macrophage dysfunction [124], reduce phagocytosis by leukocytes [137], and diminish antibody-mediated phagocytosis because of EPS matrix [138]. A 25% reduction of oxidative burst response of PMNs has been found in *P. aeruginosa* in biofilm when compared to their planktonic form [139]. Alginate (an exopolysaccharide) and rhamnolipids (glycolipids) have been found to protect the biofilm of *P. aeruginosa* from leukocyte phagocytosis [140, 141]. Mature biofilms of *C. albicans* are resistant to monocyte phagocytosis, thus show an immunosuppressive effect [142]. By secreting biofilm promoting compounds like exopolysaccharides, proteins, and other peptides, *S. epidermidis* regulates host immune responses and escapes getting killed [143]. Rhamnolipids and alginate produced by *P. aeruginosa* help in polymorphonuclear leukocyte necrosis and in evading macrophages, respectively [144]. Modulation in the deposition of immunoglobulin G (IgG) on the bacterial surfaces and activation of complement protein C3b by *S. epidermidis* provides resistance to phagocytosis, thus get escaped from the immune system and form biofilm [123, 145].

Biofilm control strategies: convenient and advanced methods to counter-attack biofilm menace

Biofilm is highly resistant to conventional antibiotics, so there is an urgent requirement to develop alternative potent therapeutic solutions to overcome the problem and improve healthcare, food safety, and other industrial sectors [11]. Chen et al. [146] classified the antibiofilm approaches into two broad categories: (a) targeting the process of biofilm formation and (b) replacing material of the substrate. The first category uses small molecules like anti-virulence compounds, e.g., CCG-203592 and CCG-205363 [147], antibiofilm compound 1 (ABC-1)—a novel benzimidazole molecule [148], and metal ion chelators including calcium chelators, e.g., trisodium citrate (TSC) and ethylene glycol tetraacetic acid (EGTA) [149]. The antibiofilm approaches also employ matrix-inhibiting enzymes like DNase I [150], proteinase K, and trypsin [151]. The second category is based on the replacement of substrate material, including medical devices, by biofilm resistant ones like using bactericidal and anti-adhesion coatings. Han et al. [152] used acidic electrolyzed water (AEW) to remove pathogenic foodborne biofilms, and they found that AEW triggers EPS disruption by deforming aromatic rings in tyrosine and phenylalanine and carbohydrate C–O–C bond. van Tilburg Bernardes et al. [153] reviewed some recent approaches for biofilm inhibition, eradication, and dispersion, viz. use of antibiofilm peptides like peptide 1018 [154], bacteriophage therapy [33] like anti-*E. faecalis* and *Enterococcus faecium* phage (EFDG1) [155], and molecules that inhibit virulence and quorum sensing signals like pilicides [156], and dihydrosventrin (DHS) [157]. Sadekuzzaman et al. [158] discussed various strategies for fighting against biofilms which include natural products like plant extracts, honey, essential oils, cumin oil, and cinnamon oil; bacteriophage; quorum sensing inhibitors; nanotechnologies like metal nanoparticles and micro- and nanoemulsions; biofilm inhibiting enzymes like deoxyribonuclease 1, lactonase, lyase, lysostaphin (LS), and α-amylase; photodynamic therapy; biosurfactants; bacteriocin; ultrasonic treatment; bioelectric approach; and some particular antibiofilm agents like capsular polysaccharides, catheter lock solution, diethylamine NONOate diethylammonium, molsidomine, xylitol, gallium, chitosan, and povidone-iodine (PVP). Gomes et al. [159] discussed the combinatorial effect of chemical (sodium hypochlorite) and mechanical stress (shear effect) against biofilms of *Acinetobacter calcoaceticus* and *Stenotrophomonas maltophilia* in drinking water distribution systems (DWDS). Pires et al. [160] reviewed the strategy of using phages with antimicrobials phage-antibiotic synergy (PAS) and their significant impact on biofilm removal. For example, the synergistic effect of using T4 phage and cefotaxime together to remove biofilm of *E. coli* ATCC 11,303 has been demonstrated [161]. Lactic acid bacteria (LAB) of genera *Lactobacillus*, *Enterococcus*, *Lactococcus*, and *Streptococcus* have been used successfully against the biofilms of *Salmonella* spp. in poultry [162]. In the meat industry, cetyltrimethylammonium bromide (CTAB) and cellulase synergistically can remove

mature biofilms of *Salmonella* spp. efficiently [163]. Aqueous and saline extracts of *Moringa oleifera* Lam. (drumstick tree) seeds have been used efficiently in eradicating biofilms of *Staphylococcus* spp. obtained from dairy effluents [164]. Leary et al. [165] analyzed the effect of different biofilm-eradicating and sterilization treatments (autoclave, sonication, saline scrub, 4% chlorhexidine (CHC) scrub) in different combinations and found a significant antibiofilm effect of autoclaving and CHC scrub combination against *S. aureus* and *S. epidermidis* biofilms from orthopedic implant materials. As biofilm formation is prominent on both biotic and abiotic surfaces like living tissues, medical devices, and food processing surfaces, it becomes important to modify the surfaces and or use inert materials to inhibit biofilm formation. Ficai and Ficai [166] mentioned different means of enhancement of antibiofilm activity through surface modifications like (a) developing new materials such as metals and alloys, polymers, ceramics, and composites, (b) modification of surfaces by physical means like reducing surface roughness by temperature curing, and (c) modification of surfaces by chemical means like antibiofilm agent immobilization, use of quaternary ammonium salts, chlorhexidine, nanoparticles, and surfactants. Biofilm formation was inhibited significantly by nanoporous (15–100 nm) anodic alumina surfaces in *E. coli*, *L. monocytogenes*, *S. aureus*, and *S. epidermidis* indicating the applications of these surfaces in the healthcare and food industry [167]. Topographic silica coatings reduced *C. albicans* biofilm formation as it was found that less biofilm formation occurred when the particle size of silica was in the range of 0.5–2.0 μm as compared to particle size in the range of 4.0–8.0 μm [168]. Gkana et al. [169] mentioned the potential use of organosilane nanoparticles as anti-adhesion and antibiofilm surface agents against various foodborne pathogens. Some novel and innovative surface modifications employed to inhibit biofilm formation include auranofin releasing antibacterial and antibiofilm polyurethane catheter coating [170], polyurethane/*Hypericum perforatum* extract (PHPE) composite [171], and fluoro-modified polypropylene films like polypropylene polyheptaflourobutyl methacrylate film (PP-PHFBM) [172]. In a recent advancement, the microbiota has been used for the eradication of microbial biofilms. Glatthardt et al. [173] reported antibiofilm activity of the bioactive molecules present in commensal *S. epidermidis* cell-free conditioned media (CFCM) against *Staphylococcus aureus* clinical isolates. It was demonstrated that *S. epidermidis* CFCM demonstrated a significant reduction in biofilm formation and enhanced disruption of established biofilms as well. Many approaches have been studied against biofilm formation and eradication; the plant-based approach is gaining much attention due to the presence of numerous active molecules which may be an alternative to antibiotics. The different current strategies to inhibit or eradicate the process of biofilm formation are represented in Fig. 2.

Plant product–based approach

From ancient times, plants are known to have medicinal value and, therefore, have been used to treat different diseases or in the preservation of food from spoilage. The antimicrobial activities of different plants have been explored exponentially to date. But now the scientists have a keen interest to find out the plant products which can effectively control biofilm formation and/or virulence factors of pathogenic microorganisms rather than killing directly [174, 175]. Several plant extracts, essential oils, and plant-based nanoformulations have been studied extensively to combat the biofilm-related problems, yet many plant products remain unexplored. Figure 3 shows different ways the plants are being used effectively against biofilm.

We know that plants like humans and animals come across pathogenic microorganisms frequently, so plants have developed a sophisticated biochemical system to defend themselves from microbial attacks. Plants act as a reservoir of metabolites broadly classified as phenolic compounds, phenolic acids, flavonoids, and terpenes that execute various pharmacological activities like antiviral, antifungal, anti-parasitic, antioxidant, antitumor, antibacterial, and anti-inflammatory. Recent studies suggest that these metabolites are effective against pathogenic biofilm-forming microorganisms even at sub-MIC concentrations [176]. As mentioned earlier, several factors play a vital role in biofilm formation and progression, so we will discuss the role of phytochemicals in the suppression, inhibition, or eradication of microbial biofilms through different mechanisms.

As discussed earlier, QS is a cell density–dependent phenomenon that controls the pathogenicity or virulence, expression of genes important for biofilm formation, and regulation of various physiological activities in most pathogenic bacteria. This change in bacterial phenotype and other physiological characters are responsible for providing the resistance of the microorganisms against antibiotic compounds. Thus, inhibition of QS could be a better option to inhibit biofilm formation as it does not affect bacterial growth, rather it suppresses the synthesis of QS molecules required for enhancing pathogenesis [177]. In this context, several studies have demonstrated that phytochemicals could be used as QS inhibitors because of their stability, effectiveness, and harmless nature. So, phytochemicals as QS inhibitors could be used for biofilm inhibition, dispersal, and eradication without exerting selective pressures on bacteria to develop resistance which is not possible in the case of known antibiotics [178, 179]. Some known QS inhibitors obtained from plants are farnesol, cinnamaldehyde,

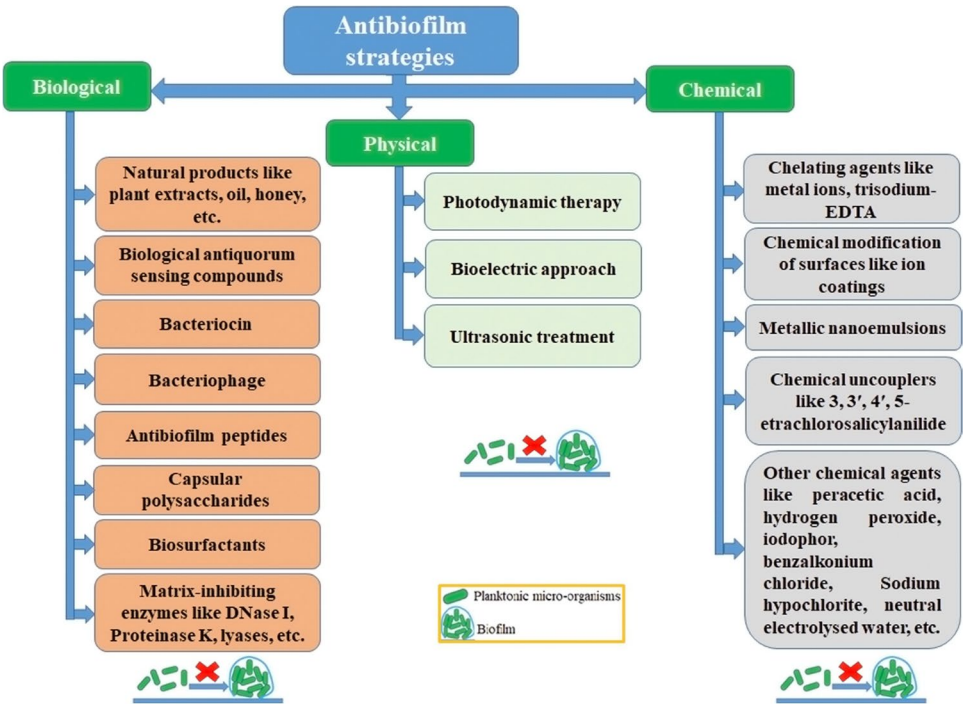

Fig. 2 Antibiofilm strategies. The different novel strategies to deal with biofilm menace could be broadly divided into three broad categories: biological, chemical, and physical strategies

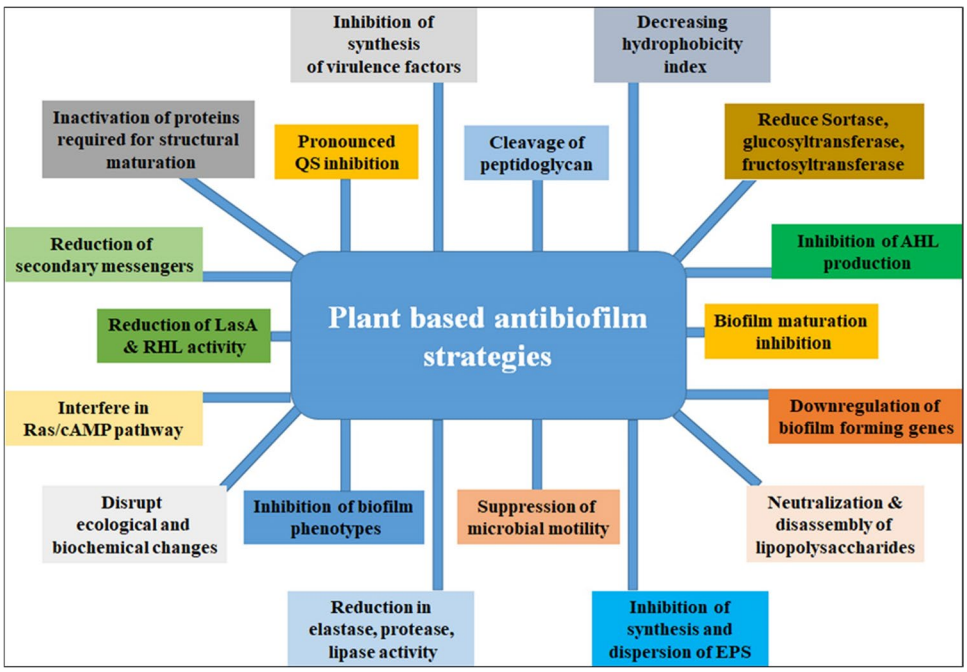

Fig. 3 Plant-based antibiofilm strategies. The figure mentions the different ways plants are being used nowadays to inhibit, reduce, or eradicate biofilm formation. As indicated in the figure, the plants act as inhibitors of quorum sensing (QS), biofilm-related enzymes, extracellular polymeric substance (EPS) matrix synthesis, virulence factors, secondary messengers, signaling cascades, biofilm promoting genes, and other biofilm-related factors. From the figure, it is clear that plants could be used effectively against microbial biofilms

resveratrol, vanillin, naringin, tannic acid, curcumin, ellagic acid, quercetin, kaempferol, etc. [180]. Since metals play a crucial role in parthenogenesis, virulence, and maintenance of biofilm, the use of phytochemicals as metal-chelators would be an effective tool to minimize biofilm formation at sub-lethal concentrations. Lin et al. [181] demonstrated the use of 1, 2, 3, 4, 6-penta-O-galloyl-b-D-glucopyranose (PGG) as an iron-chelating agent for the inhibition of biofilm formation in *S. aureus.* A calcium-chelating phytochemical, alizarin, was studied by Lee et al. [182] to demonstrate its role in inhibiting biofilm formation in *S. aureus* by quenching calcium ions. Plant extracts and/or phytochemicals employ different mechanisms to inhibit biofilm formation. Some of the studies demonstrated the role of medicinal plants to inhibit or reduce the production of biofilm which include the following: inhibition of virulence factors and

other regulatory genes (*vicR*, *relA*, *brpA*, and *comDE*) by Kaffir lime leaf extract in *S. mutans* [183]; curcumin from *Curcuma longa* inhibited elastase/protease activity, pyocyanin biosynthesis, production of acyl-homoserine lactone (HSL), and downregulated QS genes in *P. aeruginosa* [184]; reduction of swimming, swarming, and twitching motility of *Yersinia enterocolitica* by naringin from orange extract [185]; decreasing the adhesive capability of *S. aureus* to abiotic surfaces by taxodione derivative obtained from *Salvia austriaca* [186]; reducing levels of a secondary messenger, bis-(3′-5′)-cyclic dimeric guanosine monophosphate synthesis, by *Zingiber officinale* crude extract in *P. aeruginosa* [187]; reducing the synthesis of pyocyanin and 2-heptyl-3-hydroxy-4(1H)-quinolone by cinnamon bark oil in *P. aeruginosa* and *E. coli* [188]; breakdown and reduction of EPS by AgNPs and extract of *Heliotropium crispum* nanoformulation against *P. aeruginosa* and *Acinetobacter baumannii* [189]; decreasing hydrophobicity index of *E. faecalis* and *Aeromonas hydrophila* by AgNPs and *Momordica charantia* fruit extract nanoformulations [190]; decrease in hydrophobicity, glucan synthesis, and cell-to-cell adhesion of *S. mutans* by *Emblica officinalis* extract [191]; reduction of EPS synthesis by decreasing production of glycosyltransferase by *Achyranthes aspera* L. extract in *S. mutans* [192]; attenuation of QS and QS-related virulence factors of *P. aeruginosa* by *Cuphea carthagenensis* extract [178]; preventing expression of QS-regulated genes *LasIR* and *RhlIR* in *P. aeruginosa* PAO1 by iberin isolated from *Armoracia rusticana* extract [177, 193]. *Syzygium cumini*– and *Psidium guajava* L.–based silver nanoparticles are some other plant-based nanoformulations that have been reported to exhibit potent antimicrobial and antibiofilm efficiencies [194, 195].

About 70% of the population in India and a good percentage of the population in other developing countries, in the range of 40% (Columbia) to 90% (Ethiopia), rely on the traditional medicinal system as a curative approach or for improving health conditions [196]. Plants have been used in the traditional systems to cure various health issues since time immemorial and are regarded as the important source of new drugs. The use of plants as traditional and complementary medicine has gained interest as a safe alternative to maintain health and cure diseases [197]. The development of resistance of pathogenic microorganisms towards known antibiotics is pushing the researchers to introduce novel and efficient antibiofilm therapy to deal with the biofilm menace. The use of plants and/or phytochemicals as antibiofilm agents is advantageous over known antibiotics in a way that they are less expensive, have less chance of side effects, and are readily available [198, 199]. According to Kim Lewis et al. [200], the plant-derived compounds have less chance to induce resistance in microorganisms due to the reason that plants may use a different chemical strategy for the control of microbial infections, perhaps to decrease the selective pressure for developing antibiotic resistance. But, phytochemicals may also inhibit growth, in which case there would be no such advantage over known antibiotics. Besides, plants are believed to have evolved with the mechanisms of synthesizing QS-interrupting molecules for quorum quenching to treat microbial infections involved in biofilm formation [201].

Conclusion and future perspective

Over time, different strategies have been developed to inhibit the planktonic growth of microorganisms. But the rise of antibiotic ineffectiveness, multidrug-resistant microorganisms, and recalcitrant infections directed researchers to understand different aspects of microbial growth and resistance to environmental cues. Most chronic infections are associated with microbial biofilms due to their potentiality to resist the known antibiotics and survive even in harsh environmental conditions. Our knowledge regarding biofilms has increased progressively since they were noticed and defined. The major achievements include elucidation of mechanisms of biofilm formation at the molecular level, the role of secondary messengers, homoserine lactones, secreted proteins, eDNA, and other metabolites in the regulation of biofilm-related genes, and maintaining the structural integrity of biofilm. The impact of various parameters affecting biofilm formation and maintenance has been studied extensively like the effect of metal ions, environmental cues, and other physiological parameters on the development and maturation of biofilms, and the importance of EPS in nutrient cycling, gene transfer, and protection against antibiotics and immune system. Furthermore, the discovery of methods and mechanisms employed by biofilms to overcome potent antibiotics and the use of ecofriendly biological, physical, and chemical methods to destabilize the biofilm communities are also worth mentioning.

Although people are trying to combat the problems created by biofilms, we have not yet come up with any novel antibiofilm strategy. We should focus on the strategies which are efficient, ecofriendly, persistent, and cost-effective as well. In this regard, researchers are trying to develop potent antibiofilm agents from natural products and/or an amalgam of phytochemicals with other physical, chemical, or biological methods to show synergistic effect and do not contribute towards the enhancement of microbial resistance. In addition to this, development of standardized antibiofilm protocols, the requirement of in vivo validations, and further understanding of mechanisms, signaling cascades, gene regulation, and involvement of signaling molecules including secondary messengers, etc. in the establishment,

development, maturation, and dispersal of biofilms are the need of the hour.

Author contribution Muzamil Ahmad Rather had the idea of the article and drafted it; Muzamil Ahmad Rather and Dr. Kuldeep Gupta did the literature search and data analysis; and the work was critically revised by Prof. Manabendra Mandal.

Funding Financial support was provided by DBT via the DBT NER Twinning Programme vide letter No. BT/PR16149/NER/95/85/ 2015 dated January 19, 2017, and Tezpur University via memo No. DoRD/RIG/10–73/1362-A dated 19/02/2019.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval No human participants and/or animals were used in the study.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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