Chapter 25

Novel perspectives on phytochemicals-based approaches for mitigation of biofilms in ESKAPE pathogens: recent trends and future avenues

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25.1 Introduction

No doubt, the recent development in pharmaceutical sectors has revolutionized our efforts to design and synthesize potential drug molecules from different resources against several health ailments including microbial infections. On contrary, pathogenic microorganisms also undergo gradual physiological, phenotypic, and genotypic transformations to tackle the relative environmental stress associated with the regular and irrational use of antibiotics. Among the several adaptations followed by the pathogenic microorganisms in response to stress conditions, the formation of an extracellular biofilm matrix is considered as a viable opportunity for the residing microflora to explore several heterogeneous microenvironments within the matrix and could bypass the adverse environmental conditions including antibiotic stress (Schlafer & Meyer, 2017). The biofilm formation and development in pathogenic microorganisms are considered as a protective barrier not only against several environmental stresses such as altered pH, salinity, osmolarity, temperature, nutritional availability, and mechanical forces but also provide a protective response against antibiotic treatment and host cell immunity. Hence, understanding the biofilm architecture and its efficient management is considered therapeutically relevant in drug discovery pipelines (Sharma et al., 2019; Zhang, Chen, et al., 2019).

25.1.1 An introduction to biofilm and historical perspectives

Microbial biofilms, as discussed earlier, are an adaptation of microbial community toward stress environments by aggregation of microbial communities where the microorganisms tend to produce a matrix of extracellular polymeric substances (EPS) and encase themselves within the self-produced matrix (Flemming et al., 2016). The formed polymeric matrix not only functions as a protective barrier against stress conditions but also allows the attachment of sessile microbiota to several biotic and abiotic surfaces. Within the biofilm matrix, the sessile microflora resides in heterogeneous microenvironments and undergoes several adaptations including modified phenotype, altered physiological responses, and transcriptional regulations (Donlan & Costerton, 2002; Lazar, 2011). From a historical perspective, the concept of biofilm was described for the very first time in 1683. Meanwhile, the etiological role of biofilms in persistent infections was studied by Nils Hoiby way back in the 1970s. The term "biofilm" was first coined by Bill Costerton in 1978 whereas the descriptive report pertaining to empirical features of bacterial biofilms was reported in the early phases of the 2000s (Chandki et al., 2011).

As per recent studies, it was evident that approximately 80% of bacteria in the natural environment have the ability to form biofilms (Penesyan et al., 2021). Interestingly, biofilm formation not only occurs under a natural suitable environment but also under several harsh environmental conditions in terms of extensive variations in temperature, pH, salinity, pressure, nutrient availability, and other topographic factors (Shakibaie, 2018). Biofilm mode of lifestyle is considered as one of the

Recent Frontiers of Phytochemicals. DOI: https://doi.org/10.1016/B978-0-443-19143-5.00005-0

most predominant and successful modes of microbial life owing to their incidences in fossilized form for several billion years (Yin et al., 2019). Owing to the importance of biofilms in clinical and healthcare settings, biofilms are categorized as a potential biomarker in understanding the etiology of bacterial infections and their ability to abolish the role of conventional antibiotics in the management of chronic microbial infections (Vestby et al., 2020). The sessile microbial community tends to form biofilms on several biotic (e.g., tissues of the human host) and abiotic (e.g., glass, polystyrene plates, biomedical instruments) surfaces and form the foundations of chronic microbial infections and several other hospital-acquired health ailments thereby creating an arduous challenge to the current antimicrobial therapy (Müsken et al., 2010). In particular, opportunistic nosocomial pathogens with special reference to the ESKAPE group of pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* sp.) have the ability to develop persistent infections by virtue of their ability to form biofilms. It is evident from earlier research works that the nosocomial pathogens with the ability to form biofilms have a higher tendency to exhibit resistance against antibiotics as compared to their planktonic counterparts (Mah et al., 2003; Whiteley et al., 2001). The formation of recalcitrant biofilm communities involves a series of dynamic events where the EPSs forming the biofilm matrix play a pivotal role in emerging chronic infections by providing mechanical stability as well as enhancing the tolerance towards antimicrobial agents. The EPS is mainly composed of exopolysaccharides, proteins, nucleic acids (i.e., extracellular DNA), lipids, etc. (Karygianni et al., 2020). An integral part of any biofilm community is the presence of water channels which forms the circulatory system within the biofilm matrix for the efficient distribution of nutrients to the encased microcolonies and thus facilitates the rapid growth of microorganisms within the matrix (Choudhury et al., n.d.).

25.1.2 An insight into the process of biofilm formation

The formation of biofilm is no doubt a rapid but complex process with the involvement of several genetical deviations, physiological processes, metabolic alterations, phenotypic variations, and physicochemical factors. However, the process involves a simple cascade of sequential events starting from (1) initial attachment to the biotic/abiotic surfaces, (2) microcolony formation, (3) establishment of biofilm matrix, (4) maturation of biofilm matrix, and (5) dispersion of biofilms (Jamal et al., 2018; Masák et al., 2014). In the first step, microbial cells tend to attach to several biotic or abiotic surfaces using their surface appendages (i.e., flagella and pili) and other physical forces such as electrostatic interactions and Van der Waals forces. Several other factors such as adhesion-associated proteins and hydrophobicity profiles greatly enhance the attachment of microbes to different surfaces. In the subsequent step, the microflora forms an irreversible attachment to the surface by forming microcolonies within the EPS. Several microcolonies correlate with each other and in return gained positive responses in terms of substrate exchange, metabolic product distribution, and other physiological events. In the next step, called the proliferation stage, bacterial cells tend to secrete EPS, which provides a suitable environment for the bacterial cells to communicate with each other through a specific chemical signaling network for the production of several virulence factors, cytotoxic elements, and other important elements responsible for resistance against antibiotics. In the final stage, under a nutrient depletion state, the sessile bacterial cells transformed into motile planktonic forms which further initiate the process of attachment and colonize other surfaces for further initiating the biofilm infection cycle (Jamal et al., 2018; Muhammad et al., 2020). The process of biofilm dispersion is inherently associated with low levels of c-di-GMP, modification of surface adhesion properties, enzymatic degradation of polysaccharides, and disassembling of polymeric matrix (Rumbaugh & Sauer, 2020).

25.1.3 Ultrastructure of biofilm communities

The ultrastructure of bacterial biofilms is mainly composed of secreted polymeric matrix called EPS which is made up of exopolysaccharides, proteins, and lipids. In the biofilm matrix, exopolysaccharides form an extensive structural network with carbohydrates like glucose, galactose, and mannose which are the most abundant carbohydrates. The diversity of carbohydrates in biofilm matrix and their production are highly dependent upon several environmental stress conditions. The extracellular proteins and their association with exopolysaccharides are important in the maintenance of biofilm architecture and its stabilization. Apart from these components, the secretion of extracellular DNA (eDNA) also greatly facilitates the formation and development of a biofilm matrix (Rabin et al., 2015). The contribution of each of the components of EPS in biofilm formation and development is spatially different among several species of the same bacterial genus as well as among the different bacterial strains (Okuda et al., 2018). The biofilm architecture forms the basis for highly dynamic and complex biological processes of the embedded heterogenic bacterial population which ultimately control the several pathophysiological events in bacterial pathogenicity. For example, prior to biofilm maturation, a highly specific and cell density-dependent chemical signaling network termed "quorum sensing" (QS)

functions to communicate among the embedded bacterial population (both intraspecies as well as interspecies communication) for survival during stress and production of several virulence phenotypes responsible for chronic infections (Schilcher & Horswill, 2020).

25.1.4 Impact of bacterial biofilm

The biofilm mode of lifestyle has enabled the residing bacterial community to behave socially and function cordially similar to that of differentiated cells in multicellular organisms. Thus, biofilm formation positively controls the infection modulatory behaviors of the embedded bacterial community (Penesyan et al., 2021). The social and collective behavior within the biofilm matrix, however, allows the tendency of nosocomial pathogens to form recalcitrant biofilms resulting in the occurrence of several chronic infections, including cystic fibrosis, chronic pneumonia, periodontitis, and other hospital-acquired infections. As per recent reports, biofilms are generally associated with several life-threatening diseases associated with different organs of the human body. For example, otitis media (auditory organs), atherosclerosis (cardiovascular system), wound infections (skin, integumentary system), cystic fibrosis (respiratory system), bacterial vaginosis (reproductive system), urinary tract infections (urinary system), etc., are associated with biofilm communities and create a global health issue (Vestby et al., 2020). Several bacterial species also harbor the oral environment and also have the tendency to form biofilms on the oral microenvironment (i.e., dental plaques by *Streptococcus mutans*) and critically affect oral health by producing dental caries and periodontal diseases (Abebe, 2021). As per estimates, biofilm-associated chronic infections result in more than 0.5 million deaths annually across the globe which ultimately results in a decrease in the global economy (Banerjee et al., 2020). Moreover, the biofilms also result in varied infections associated with indwelling biomedical devices such as catheters, heart valves, orthopedic devices, dental implants, peritoneal dialysis catheters, surgical soft tissue prostheses, and contact lenses thus inferring several consequences in terms of health as well as the economy (Borges et al., 2016; Stoica et al., 2017). Thus, biofilms on implanted medical devices are the root cause of the majority of hospital-acquired infections leading to several life-threatening conditions (Dufour et al., 2010).

Food industries and food processing sectors are highly prone to the growth and attachment of pathogenic microorganisms and initiate the process of biofilms. Hence, the incidence of biofilm communities on food surfaces and the devices associated with food processing units result in an increased incidence of food safety risks, health ailments, and severe economic loss. Since biofilm modes of lifestyle are difficult to handle using conventional therapeutics and disruption strategies; the development of biofilms in food-based industries has resulted in severe disease outbreaks associated with foodborne pathogenic bacteria (Abebe, 2020). For example, biofilm-forming *Bacillus cereus* has the ability to withstand the industrial pasteurization process by forming endospores, and thus, it is difficult to remove this bacteria using conventional microbial cleaning approaches. In addition, some bacterial strains under severe stress have the ability to produce several types of diarrheal enterotoxins which ultimately result in the occurrence of diarrhea and food poisoning (Galie et al., 2018).

25.2 Biofilm-mediated drug resistance in ESKAPE pathogens

In the last few decades, antimicrobial resistance (AMR) became a global health issue with an annual death of 0.7 million people across the globe. As per the estimation of the WHO, if we fail to tackle the AMR phenomena, it is expected to cause 10 million deaths by 2050 with a global burden of USD 100 trillion. Among the several factors responsible for the occurrence of AMR, the ability of pathogenic microorganisms to form protective measures in the form of biofilms gained recent recognition. The biofilm formation provides an aided advantage to the bacterial pathogens to exhibit collective recalcitrance for withstanding the wrath of high concentrations of antibiotics. For example, about 80% of chronic and persistent microbial infections are directly associated with biofilm dynamics, which ultimately bypass the antibiotic treatment regimens (Uruén et al., 2021). Within the biofilm matrix, the gradients in the distribution of nutrients, osmotic pressure, salinity, and oxygen result in the spatial heterogeneity of the bacterial population which strongly influences the relative fitness benefits of the cooperative and competitive phenotypic bacterial population. This spatial arrangement within a biofilm is observed in both monospecies as well as multispecies biofilms (Nadell et al., 2016). The physiological stratification and phenotypic heterogeneity observed within the biofilm matrix are responsible for the generation of a gradient of the bacterial population exhibiting genetic and heritable variations (termed as "resistance"), non-inheritable behavior (termed as "tolerance"), and altered physiological behaviors in response to stress (termed as "persistence"). The bacterial population exhibiting "resistance" could grow even at the exposure to high doses of antimicrobial treatment irrespective of the duration of the treatment regimens. Meanwhile, the bacterial population showing "tolerance" infers a transient ability to sustain antimicrobial therapy. In addition, a subpopulation within the clonal bacterial population exhibits "persistence," where the bacterial community becomes dormant on exposure to antibiotics and persists for a longer time (Brauner et al., 2016; Flemming et al., 2016).

The biofilm-mediated resistance to antibiotics in ESKAPE pathogens occurs through several mechanisms including extracellular matrix-mediated restriction of antibiotic penetration, increased production of hydrolyzing enzymes specific to antibiotics, alteration in pathophysiological targets, increased subpopulation of persister cells within the matrix, physiological dormancy with differential metabolic activities, biofilm-mediated upregulation of bacterial efflux machinery, enhanced horizontal gene transfer among the embedded bacterial population, and matrix-mediated binding retardation of antibiotics (De Oliveira et al., 2020; Høiby et al., 2011). The extracellular matrix composition in biofilm architecture also greatly establishes the cross-talk between embedded bacterial communities with an increased rate of genetic material exchange. In this cross-talk, antibiotic resistance gene clusters also tend to disperse among the bacterial population which concomitantly facilitates survival strategies against exposure to antibiotics (Uruén et al., 2021). For instance, the presence of polyanionic alginate in EPS of *P. aeruginosa* biofilm provides a protective environment to the embedded bacterial population against the aminoglycoside group of antibiotics (Uruén et al., 2021). The increased production of extended-spectrum β-lactamase (ESBL) and carbapenemase like metallo-β-lactamase (MBL) in ESKAPE pathogens has critically enabled the resistance to next-generation antibiotics including carbapenems. Similarly, the production of aminoglycoside-modifying enzymes highly contributed to resistance to aminoglycoside antibiotics in *A. baumannii* (Gedefie et al., 2021; Pandey et al., 2021). Since the majority of antibiotics specifically target actively dividing microbial cells, the occurrence of persister cells with phenotypic heterogeneity and metabolic dormancy within biofilms becomes less susceptible to antibiotics. Similarly, the occurrence of anoxic conditions within the biofilm matrix also critically affects the functional attributes of certain antibiotics which require aerobic metabolic activities as their target sites (Varadarajan et al., 2020).

25.2.1 Regulation of specific virulence genes associated with biofilms

As mentioned earlier, approximately 40%−80% of the bacterial population inherently produce biofilms. In particular, ESKAPE pathogens gained considerable attention owing to their widespread virulence attributes and ability to induce chronic infections through biofilm formation. The transcriptomic studies have revealed that regulatory gene expression in the planktonic state resembles that of the biofilm state. The only difference observed in biofilm mode is the regulatory adaptations in terms of physiological and metabolic processes. However, the regulatory genes which are generally associated with the adaptive conditions for anaerobic growth conditions are observed to be comparatively upregulated when the planktonic form transforms into a sessile state during biofilm development (Høiby et al., 2011). Quorum sensing (QS), the highly synchronized and complex cell-to-cell communication, is considered the control center for coordinating several socialistic behavior and pathophysiological processes in response to regulated synthesis, sensing, and response to signaling molecules. It is evident from earlier studies that QS regulatory network plays a pivotal role in biofilm formation and development by modulating the production of several virulence phenotypes such as EPS, alginates, rhamnolipids, cytotoxic elements, hydrophobicity factors, surface motility accessories (i.e., pili, flagella, and fimbriae), pellicle formation, eDNA, and adhesion proteins (Chang, 2018; Lazar et al., 2021; Rutherford & Bassler, 2012; Schiessl et al., 2019; Tahrioui et al., 2019).

The presence of *psl* gene (encoding mannose-rich exopolysaccharides) in the extracellular matrix of multidrug-resistant ESKAPE pathogen, *P. aeruginosa*, acts as first line of defense against exposure to antibiotics during the early stages of biofilm formation (Billings et al., 2013; Joo & Otto, 2012). Further, *Psl* polysaccharides induce the production of c-di-GMP (key secondary messenger), which drives the phenotypic switching of bacterial cells from planktonic to biofilm state. Hence, c-di-GMP is considered an important phenotype in biofilm development (Dragoš & Kovács, 2017). The key regulatory signal molecules including acyl homoserine lactones (AHLs) in gram-negative bacteria, autoinducer peptides (AIPs) in gram-positive bacteria, and interspecies signal analogues (e.g., diffusible signal factors (DSFs)) are also involved in biofilm maturation and dispersion (An et al., 2019; McDougald et al., 2012). Since biofilm regulatory signals are responsible for inducing bacterial virulence in chronic microbial infections, it is imperative to develop therapeutic modules with an aim to disrupt the biofilm formation and eradication of the formed biofilm matrix.

25.3 Mitigation of biofilm architecture: current therapeutic trends

During the dispersion phase, biofilm-encased bacterial communities egress from the matrix and enter planktonic mode which is considered as most vulnerable to therapeutic regimes; the post-dispersion phase is considered a therapeutic target for biofilm control approaches (Rumbaugh & Sauer, 2020). Presently, several conventional and alternative therapeutic regimens are considered as control measures against biofilms-associated infections. In particular, bacteriophage

therapy, mechanical eradication of biofilm by physical techniques, biophysical approaches for improved drug penetration into the biofilm matrix, improved drug delivery systems with localized drug delivery, development of QS inhibitors (QSIs) and anti-biofilm molecules, modified vaccine development targeting biofilm adhesive phenotypes, development of matrix destabilizing agents, mechanistic development of anti-persister strategies, and development of next-generation medical devices with decreased susceptibility to microbial biofilms are considered as promising biofilm control measures (Lazar et al., 2021). Owing to the infection severity of multispecies biofilms, putative drug candidates (i.e., QSIs and anti-biofilm agents) along with a combination of enzymatic treatment regimens could be inevitable in the inhibition and eradication of biofilms (Willems et al., 2016).

The recent development of electroceutical dressings provides novel avenues for the remediation of formed biofilm matrix by using electric fields and concomitantly improving the wound healing process (Dusane et al., 2008). The emergence of novel nano-scaled drug delivery systems is also being spatially designed and developed for the mitigation and eradication of microbial biofilms. Among the spatially designed drug delivery nanoplatforms, polymeric nanoparticles, inorganic nanoparticles, dendrimers, and lipid-based vesicular nanoparticles (i.e., liposomes) are considered as influential in escaping biofilm-mediated drug resistance by critically improving the localized delivery of loaded drug molecules at the target sites (Rukavina & Vanić, 2016). As per the recent trends, pharmacologically relevant natural products and their derivatives gained considerable attention in our efforts in the management of QS-mediated biofilm mechanics in ESKAPE pathogens.

25.3.1 Synthetic and semisynthetic derivatives as biofilm inhibitors

The semisynthetic derivatives (amide derivatization) of di-rhamnolipids (derived from *Lysinibacillus* sp. BV152.1) significantly improved the biofilm inhibition against ESKAPE pathogens, *P. aeruginosa* PAO1 and *S. aureus*. Among the amide derivatives, the morpholine derivative exhibited the highest effect on biofilm disruption (Aleksic et al., 2017). Due to the pharmacological importance of antimicrobial peptides in biofilm mitigation, semisynthetic peptide lin-SB056−1 and its dendrimeric derivative (lin-SB056−1)$_2$-K were evaluated for their anti-biofilm properties. As compared to the parent molecule, the dendrimeric derivative exhibited promising anti-biofilm effects against both reference strain, *P. aeruginosa* PAO1 as well as cystic fibrosis lung isolates of *P. aeruginosa* (Grassi et al., 2019). In an earlier study, chalcone-linked amine derivative ((E)-N-(4-(3-(4-chlorophenyl)acryloyl)phenyl)-3-(piperidin-1-yl)propanamide) showed potent anti-biofilm activities against *S. aureus* IFO 3060 and *P. aeruginosa* IFO 3448 by modulating the c-di-GMP signaling (El-Messery et al., 2018). Recently, synthetic derivatives of hydroxynaphthoquinone (2-hydroxy-1,4-naphthoquinone) exhibited promising biofilm inhibition potential against methicillin-resistant *S. aureus* (MRSA) and thus could be considered for clearance of antibiotic resistance phenomenon (Song et al., 2020). In a recent study, a synthetic benzoyl ester derivative of β-amyrin (e.g., β-amyrin 3,4,5-trimethoxybenzoyl ester) exhibited a significant inhibitory effect on biofilm formation in *S. aureus* (Tamfu et al., 2022).

No doubt, synthetic and semisynthetic compounds exhibit promising avenues in the management of biofilm dynamics; their probable toxicity profile, bioavailability, and biodegradability issues limit their widespread potential as anti-biofilm agents. In this context, scientific interventions have shifted toward more reliable natural resources as potential alternatives in the regulation of biofilm mechanics and drug resistance phenomena. Natural resources, particularly plant-derived phytochemicals and microbes-derived secondary metabolites, received worldwide scientific attention for their pharmacological relevance and could be considered as reliable and effective therapeutic regimens in the fight against chronic biofilm infections and drug resistance-associated health hazards.

25.3.2 Microbial secondary metabolites for biofilm inhibition

Microbial-derived bioactive molecules are considered pharmacologically important candidates in the management of biofilm formation in ESKAPE pathogens. Azithromycin (AZM), an important macrolide antibiotic derived from *Saccharopolyspora erythraea*, transcriptionally not only downregulated the expression of QS regulatory system in *P. aeruginosa*, but also critically reduced the expression of multiple flagellar biosynthesis proteins required for biofilm surface attachment (Townsley & Shank, 2017). The presence of bioactive secondary metabolites such as Fenaclon, 2,4-di-tert-butylphenol, 1,4-phenylenediacetic acid, 4-ethoxybenzaldehyde, 3-isobutylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione present in fungal crude extracts of *Diaporthe phaseolorum* SSP12, *Aspergillus ochraceopetaliformis* SSP13, and *Phomopsis tersa* have significantly contributed in attenuation of the QS regulatory virulence phenotypes production and biofilm formation in *P. aeruginosa* PAO1 (Meena et al., 2020; Pattnaik, Ahmed, et al., 2018; Pattnaik, Ranganathan, et al., 2018).

25.4 Phytochemicals-based mitigation strategies against biofilm formation

Among the alternative therapeutic drug candidates from natural resources, plants and plant-derived phytochemicals are considered to be the most explored resources due to their easy availability, comparatively less complex extraction procedures, and absence of biological threats unlike that of microbial resources. The rich lineage of biologically active, structurally diverse phytochemicals identified from plant sources is inherently reported for widespread pharmacological potential such as antimicrobial, anticancer, anti-inflammatory, antidiabetic, antioxidant, neuroprotective, hepatoprotective, and cardioprotective properties (Fatima et al., 2021; Khare et al., 2021; Mitra et al., 2022; Song et al., 2022). Owing to their extensive pharmacological and pharmaceutical importance, phytochemicals are considered effective avenues for disease prevention and treatment against chronic microbial infections (Yu et al., 2021).

25.4.1 Crude plant extracts against biofilm formation in ESKAPE pathogens

In the fight against chronic microbial infections, no doubt antibiotics serve as potential therapeutic agents, but the emergence of resistance to these antimicrobial drugs has urged the scientific community to look for alternative yet effective therapeutic measures to cope with the microbial infections and drug resistance. In this context, pharmacologically relevant plant resources and the derivatized products could be instrumental in providing a rational strategy to counteract drug resistance by targeting the bacterial communication system (Ouedraogo & Kiendrebeogo, 2016). Medicinal plants are a rich source of bioactive secondary metabolites which significantly contribute toward the use of the plant materials as folkloric medicines for several diseases and disorders. Due to the comparatively low toxicity profile and absence of bioavailability issues, plant-derived products are considered for therapeutic applications in the fight against microbial infections and biofilm-mediated drug resistance. Since the beginning of the 21st century, a large number of medicinal plants and rare medicinal plants are being actively screened for their ability to attenuate bacterial signaling networks which are associated with bacterial pathogenesis and drug resistance (Banerjee et al., 2017). Table 25.1 depicts the list of crude plant extracts and their bioactive fractions reported for inhibition of QS-regulated virulence and biofilm formation in ESKAPE pathogens (Table 25.1).

25.4.2 Phytochemicals involved in the inhibition of biofilm formation in ESKAPE pathogens

Since ancient times, ethnopharmacologically important medicinal plants and their bioactive phytochemicals have been recognized as rich sources of folkloric medicines against several pathogenic microorganisms (Elhawary et al., 2018). The presence of structurally diverse phytochemicals such as alkaloids, flavonoids, anthocyanins, anthraquinone, polyphenols, organosulfur compounds, tannins, terpenes, terpenoids, phenolic acids, etc., in the ethnobotanically important plants has characteristically modulate widespread pharmacological properties (Haripriyan et al., 2018; Qais et al., 2019). Plant-derived phytochemicals are considered as preferred alternatives in the development of potential QSIs and anti-biofilm agents due to their relatively nontoxic nature, biocompatibility, easy availability, biodegradability, and eco-friendly nature (Ghosh et al., 2022; Li et al., 2018). For example, bioactive phytochemicals such as caffeine, estragole, squalene, and neophytadiene identified from ethyl acetate fraction of *Camellia sinensis* potentially modulate the QS transcriptional regulators in *P. aeruginosa*. Thus, these compounds could be considered as potential inhibitors of QS-regulated virulence and biofilm formation (Qais et al., 2019). Similarly, flavonoid-rich *Citrus* sp. reported for the presence of naringin, naringenin, quercetin, kaempferol, apigenin, baicalein, etc., evidently exhibited promising inhibitory effect on QS-mediated production of virulence phenotypes and biofilm (Liu et al., 2017; Peng et al., 2019). The promising antibacterial properties of simple phenols, polyphenols, phenolic acids, and coumarin derivatives are considered in the development of phenolic acids and polyphenols as potential regulators of QS-associated biofilm mechanics (Lemos et al., 2014; Mombeshora et al., 2021).

Similarly, the presence of bioactive quinone derivatives as well as terpenes in *Nigella sativa* extracts resulted in the inhibition of biofilm formation in ESKAPE pathogens (*P. aeruginosa*, *K. pneumoniae*, and *S. aureus*) and hence could be considered in the treatment of drug-resistant infections (Rahman & Roy, 2021). The plant-derived essential oil compounds such as thymol, carvacrol, and geraniol also possess promising antimicrobial and anti-biofilm activities against ESKAPE uropathogen, *K. pneumoniae*. This result suggested the use of essential oil compounds as a putative source of anti-biofilm agents in the fight against chronic microbial infections (Kwiatkowski et al., 2022). Plant-derived essential oil exhibited promising aspects in targeting several pathophysiological mechanisms associated with drug resistance. For example, interference in a cell density-dependent QS regulatory network, cell membrane permeability, drug efflux pumps machinery, transfer of mobile genetic elements, and biofilm mechanics are possible therapeutic targets in the fight against persistent microbial infections and drug resistance (Khare et al., 2021). The list of phytochemicals reported for QS attenuation and biofilm inhibition in ESKAPE pathogens is listed in Table 25.2.

TABLE 25.1 List of pharmacologically relevant medicinal plants reported for quorum sensing inhibition and mitigation of biofilm mechanics against ESKAPE pathogens.

SI. No.	Plant species	Plant family	Target microorganism	Minimum inhibitory concentrations (MIC)	Mechanism of action	References
1.	*Amomum tsao-ko*	Zingiberaceae	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	2, 1 mg/mL, respectively	Inhibition of biofilm formation by modulating QS response	Rahman et al. (2017)
2.	*Andrographis paniculata*	Acanthaceae	*P. aeruginosa*	5 mg/mL	Modulation of QS-regulated virulence phenotypes production, biofilm inhibition, and interference in pathogen-induced activation of MAPK pathway	Banerjee et al. (2017)
3.	*Anogeissus leiocarpus* (DC) Guill. et Perr.	Combretaceae	*P. aeruginosa* PAO1	1.25 mg/mL	Suppression of QS regulatory genes	(Ouedraogo and Kiendrebeogo, 2016)
4.	*Cornus controversa*	Cornaceae	*P. aeruginosa* PAO1	>2%	Anti-biofilm and QS inhibitory properties	Choi et al. (2018)
5.	*Cassia alata* L.	Caesalpiniaceae	*P. aeruginosa*	–	Interference in the production of QS-associated pathogenic factors and inhibition of bacterial motility	Rekha et al. (2017)
6.	*Centella asiatica*	Apiaceae	*P. aeruginosa* PAO1	>400 μg/mL	Inhibition of QS-regulated pathogenic factors production, swarming motility, and biofilm formation	Vasavi et al. (2016)
7.	*Malva sylvestris*	Malvaceae	ESKAPE pathogens (*S. aureus*, *Klebsiella pneumoniae*, and *Enterococcus faecalis*)	BIC_{50} (minimum biofilm inhibition): 40 mg/mL	Inhibition of biofilm formation	Fathi et al. (2022)
8.	*Mangifera indica*	Anacardiaceae	*P. aeruginosa* PAO1	>0.8 mg/mL	Concentration-dependent inhibition of QS-mediated virulence factors production and biofilm formation	Husain et al. (2017)
9.	*Laserpitium ochridanum*	Apiaceae	*P. aeruginosa* and *S. aureus*	0.5 and 0.4 mg/mL respectively	Inhibition of biofilm formation and decreased production of QS-mediated virulence factors	Mileski et al. (2017)
10.	*Carum copticum*	Apiaceae	*Acinetobacter baumannii*, *K. pneumoniae*	25 mg/mL	Disruption of biofilm formation with the highest effect was observed against *A. baumannii*	Mohammadi et al. (2019)
11.	*Syzygium jambos* (L.) Alston	Myrtaceae	*P. aeruginosa* PAO1	1 mg/mL	QS inhibition and biofilm disruption	Rajkumari et al. (2018)

(*Continued*)

TABLE 25.1 (Continued)

SI. No.	Plant species	Plant family	Target microorganism	Minimum inhibitory concentrations (MIC)	Mechanism of action	References
12.	*Syzygium cumini* (L.) ethyl acetate fraction	Myrtaceae	*P. aeruginosa* and *S. aureus*	–	Inhibition of QS regulatory virulence and biofilm formation	Gupta et al. (2019)
13.	*Parkia javanica*	Fabaceae	*P. aeruginosa*	180 μg/mL	Attenuation of QS-mediated swarming motility, secretion of virulence factors, and biofilm formation	Das et al. (2017)
14.	*Pistacia atlantica*	Anacardiaceae	*P. aeruginosa*	0.5 mg/mL	Inhibition of QS-regulated virulence by targeting transcription regulator, LasR	Kordbacheh et al. (2017)
15.	*Solanum torvum*	Solanaceae	*P. aeruginosa*	–	Disturbance in bacterial virulence at sublethal concentration	Vadakkan et al. (2019)
16.	*Psoralea corylifolia*	Fabaceae	*P. aeruginosa*	>1 mg/mL	Inhibition of QS-regulated virulence factors by modulating stable interaction with transcriptional regulators, LasR and RhlR	Husain et al. (2018)
17.	*Terminalia bellirica*	Combretaceae	*P. aeruginosa*	>0.5 mg/mL	Reduction of biofilm formation by interfering the QS regulatory behavior	Sankar Ganesh and Ravishankar Rai (2018)
18.	*Salvadora persica*	Salvadoraceae	*Staphylococcus* sp.	6.25 mg/mL	Biofilm inhibition	Noumi et al. (2017)
19.	*Herba patriniae*	Caprifoliaceae	*P. aeruginosa*	–	Downregulation of biofilm-associated genes	Fu et al. (2017)
20.	*Galla chinensis*	Anacardiaceae	*P. aeruginosa* PAO1	2 mg/mL	Inhibition of QS-mediated swarming motility	Zhang, Djakpo, et al. (2019)
21.	*Hypericum perforatum*	Hypericaceae	*P. aeruginosa* PAO1	–	Downregulation of QS-regulated virulence phenotypes by modulating QS signaling pathway	Doğan et al. (2019)

TABLE 25.2 List of plant-derived phytochemicals reported for attenuation of quorum sensing-regulated virulence and biofilm inhibition against ESKAPE pathogens.

SI. No.	Chemical class	Phytochemicals	Plant source	Target microorganisms	Minimum inhibitory concentration (MIC)	Mechanism of action	References
1.	**Alkaloids**	Berberine	*Berberis* sp.	*Pseudomonas aeruginosa* PAO1	1.25 mg/mL	Targets RhlR of QS circuit and modulates biofilm mechanics	Aswathanarayan and Vittal (2018)
2.		Hordenine	*Hordeum vulgare*	*P. aeruginosa* PAO1	2.5 mg/mL	Suppression of QS regulatory genes and biofilm formation	Zhou et al. (2018)
3.		Reserpine	*Rauwolfia serpentina*	*P. aeruginosa* PAO1	0.8 mg/mL	Inhibition of QS-mediated virulence phenotypes, biofilm disruption, and motility	Parai et al. (2018)
4.		Caffeine	*Coffea arabica*	*P. aeruginosa* (MTCC 424)	200 μg/mL	Biofilm disruption by interfering QS machinery without affecting the cell viability	Chakraborty et al. (2020)
5.	**Anthocyanins**	Proanthocyanidins	*Vaccinium macrocarpon* L.	*P. aeruginosa* PA14	–	Inhibition of QS-controlled virulence determinants	Maisuria et al. (2016)
6.		Anthocyanidins (delphinidin and pelargonidin)	–	*P. aeruginosa* PAO1	0.45 mg/mL	Biofilm disruption	Pejin et al. (2017)
7.	**Anthraquinones**	Aloe-emodin	*Rheum officinale* Baill.	*Staphylococcus aureus*	>1.024 mg/mL	Biofilm inhibition by decreasing the production of extracellular proteins and polysaccharide intercellular adhesion (PIA)	Xiang et al. (2017)
8.		Alizarin (1,2-dihydroxyanthraquinone)	–	Methicillin-sensitive *S. aureus* (MSSA 6538)	>1 mg/mL	Promotion of anti-biofilm activity by inhibition of hemolytic activity	Lee et al. (2016)
9.		Symploquinone A,C	*Symplocos racemosa* Roxb.	Methicillin-resistant *S. aureus* (MRSA)	83–160 μg/mL	Inhibition of biofilm formation at sub-MICs	Farooq et al. (2017)

(*Continued*)

TABLE 25.2 (Continued)

SI. No.	Chemical class	Phytochemicals	Plant source	Target microorganisms	Minimum inhibitory concentration (MIC)	Mechanism of action	References
10.	**Flavonoids and polyphenols**	Baicalein	*Scutellaria baicalensis*	*P. aeruginosa*, *S. aureus* 17546	0.256 mg/mL,	Attenuation of QS-mediated virulence phenotypes and biofilm disruption	Chen et al. (2016), Luo et al. (2016)
11.		Quercetin glucopyranoside	*Allium cepa*	*P. aeruginosa*	0.4 mg/mL	Modulation of QS-regulated response	Al-Yousef et al. (2017)
12.		Trihydroxyflavone	*Alstonia scholaris*	*P. aeruginosa*	0.2 mg/mL	Disruption of biofilm matrix by targeting the QS circuit, LasR	Abinaya and Gayathri (2019)
13.		Calycopterin	*Marcetia latifolia*	*P. aeruginosa* (ATCC 27853)	EC_{50}: 34 μM	Inhibition of QS-mediated pyocyanin production and swarming motility	Froes et al. (2020)
14.		Baicalin	*Scutellaria baicalensis*	*P. aeruginosa*	>1.024 mg/mL	Biofilm inhibition	Luo et al. (2017)
15.		Curcumin	*Curcuma longa*	*Acinetobacter baumannii*	>500 μg/mL	Disruption of biofilm formation by inhibition of pellicle formation and surface motility properties	Raorane et al. (2019)
16.		Pulverulentone A	*Callistemon citrinus*	Methicillin-resistant *S. aureus*	125 μg/mL	Attenuation of QS machinery and biofilm inhibition	Shehabeldine et al. (2020)
17.		Fisetin, phloretin	–	*Acinetobacter baumannii*	>500 μg/mL	Inhibition of pellicle formation and biofilm formation	Raorane et al. (2019)
18.		Resveratrol	–	*P. aeruginosa*	>400 μM	Inhibition of QS-regulated phenotypes by minimizing oxidative stress	Chen et al. (2017)
19.		Naringenin	–	*P. aeruginosa*	–	Competitively inhibited the binding of C_{12}-HSL for binding to its cognate LasR receptor and thus disrupted the expression of QS-regulated virulence genes	Hernando-Amado et al. (2020)
20.		Scutellarein	*Scutellaria lateriflora*	*S. aureus*	500 μg/mL	Inhibition of biofilm-associated protein (BAP)-mediated biofilm formation	Matilla-Cuenca et al. (2020)

21.	**Phenylpropanoids**	Cinnamic acid	*Averrhoa carambola*	*P. aeruginosa*	0.5 mg/mL	Impairment of QS-controlled pathogenesis	Rajkumari et al. (2018b)
22.		Cinnamaldehyde	*Cinnamomum* sp.	*P. aeruginosa*	>11.8 mM	Modulates c-di-GMP signaling and promotes biofilm disruption	Topa et al. (2018)
23.		Chlorogenic acid	*Camellia sinensis*	*P. aeruginosa*, *S. aureus*	>5 mg/mL	Inhibits QS-regulated pathogenic factors and biofilm dynamics	Wang et al. (2019)
24.		Eugenol	*Syzygium aromaticum*	*P. aeruginosa* PAO1	275 μg/mL	Controls production of QS-regulated pathogenic factors	Rathinam et al. (2017)
25.		6-Gingerol	*Zingiber officinale*	*P. aeruginosa*	–	Reduces the QS regulatory response	Kim et al. (2015)
26.		Ferulic acid	-	*P. aeruginosa* PAO1	1 mg/mL	Inhibition of biofilm formation by modulating the production of exopolysaccharides	Pattnaik, Barik, et al. (2018)
27.	**Organosulfur compounds**	Ajoene	*Allium sativum*	*P. aeruginosa*	–	Alters biofilm architecture, rhamnolipid inhibition	Jakobsen et al. (2012)
28.		Allicin	*A. sativum*	*P. aeruginosa*	–	Disruption of the bacterial adhesion in the initial stages of biofilm formation by inhibition of EPS production	Xu et al. (2019)
29.	**Terpenes and terpenoids**	(+)-Dehydroabietic Acid	Coniferous plants	*S. aureus*	70 μM	Inhibition of biofilm matrix	Fallarero et al. (2013)
30.		Tormentic acid congener	*Callistemon viminalis*	*P. aeruginosa*, *S. aureus*	25 and 12.5 μg/mL	Biofilm disruption by decreasing the release of eDNA and capsular polysaccharides from biofilms	Chipenzi et al. (2020)
31.		Betulin and betulinic acid	*Syzygium jambos*	*P. aeruginosa*	250 μg/mL	Interferes with QS-mediated virulence and biofilm architecture	Rajkumari et al. (2018a)
32.		Carvacrol	*Origanum vulgare*	*P. aeruginosa*	>3.9 mM	Targets LasI and modulates QS-controlled behavior	Tapia-Rodriguez et al. (2019)
33.		Phytol	Plant chlorophyll	*P. aeruginosa*	19 μg/mL	Alters bacterial motility profile	Pejin et al. (2015)

(*Continued*)

TABLE 25.2 (Continued)

SI. No.	Chemical class	Phytochemicals	Plant source	Target microorganisms	Minimum inhibitory concentration (MIC)	Mechanism of action	References
34.	**Terpenes and terpenoids**	Phytol	–	*Klebsiella pneumonia* (ATCC BAA-1705; ATCC 700603)	0.125 mg/mL	Reduction of adhesion capabilities of hypervirulent and drug-resistant *K. pneumoniae* by disruption of biofilm architecture	Adeosun et al. (2022)
35.		Terpinen-4-ol	*Pandanus odorifer* essential oil	*P. aeruginosa*	0.5% (v/v)	Mitigation of QS regulatory behaviors in *P. aeruginosa* by targeting transcriptional regulators, LasR, RhlR, and PqsR; downregulation of QS-regulated genes; biofilm inhibition	Bose et al. (2020)
36.		Glycyrrhetinic acid	*Glycyrrhiza glabra*	*P. aeruginosa*	160 μg/mL	Inhibits the secretion of pathogenic determinants and biofilm formation	Kannan et al. (2019)

25.5 Current trends in biofilm inhibition

25.5.1 In silico approaches for phytochemicals-based mitigation of biofilm formation

The interdisciplinary aspects of computational tools in determining the effectiveness of putative drug candidates from natural resources have revolutionized the current drug discovery and development pipelines. Particularly, computer-aided drug design (CADD) using the molecular docking and molecular dynamics simulation (MDS) tools provide a fast and cost-effective screening of thousands of putative drug candidates against either predefined pathophysiological targets or novel undefined targets. As a result, potential drug-like molecules could be easily filtered and evaluated for their possible role in the mitigation of pathophysiological responses (Abelyan et al., 2020; Wei et al., 2016; Zeng et al., 2018). In the development of potent QSIs and anti-biofilm agents from natural resources against ESKAPE pathogens, the CADD-based *in silico* approaches provide an insight into the possible mechanism of action. Based on the computational trends, further therapeutic regimens in vitro and in vivo could be decided for the establishment of their candidature as potential inhibitors of QS-mediated virulence and biofilm formation (Adnan et al., 2020; Awadelkareem et al., 2022). Since QS regulatory network is highly dependent on the activation of specific transcriptional regulators (i.e., LasR, RhlR), targeting these regulators could be instrumental in disrupting the QS signaling network. In this regard, CADD approaches provide a virtual platform to define the interactions of the putative drug candidates with the therapeutic regulators. Based on the stability of the interaction, novel candidates could be selected for their efficacy in minimizing the QS transcriptional regulator-mediated virulence and biofilm formation. For example, the stable interactions of bioactive phytochemicals such as mosloflavone, 5-hydroxymethyl furfural (5-HMF), betulin, and cinnamic acid toward QS transcriptional regulators, LasR and RhlR in *P. aeruginosa* PAO1, were evident from molecular docking and molecular dynamic simulation. The *in silico* results were further corroborated through in vitro studies which revealed the significant alteration in the production of virulence phenotypes linked to QS circuit and biofilm formation (Hnamte et al., 2019; Rajkumari et al., 2018a, 2018b, 2019).

Since bacterial biofilms are highly resistant to antibiotics and the limitations associated with available antibiotics, it is highly important to optimize the doses of conventional antibiotics. In this context, pharmacokinetic (PK) and pharmacodynamic (PD) prediction of antimicrobial agents through computational tools could provide cues to improve the biological effect on drug-resistant pathogens. In recent studies, comparative PK and PD profiles of antimicrobials against both planktonic and biofilm-embedded sessile bacteria were predicted through computational tools, which could facilitate upliftment in the scientific efforts in drug optimization before the treatment regimens (Wu et al., 2015). Since PK/PD profile is an essential norm for putative drug candidates before being considered for market approval, advanced computational tools such as SwissADME, admetSAR, TOPKAT module of Discovery Studio, etc., are actively engaged in predicting several parameters associated with PK/PD properties. The drug candidates after being passed through the PK/PD filters could be considered for further evaluation (Alam & Khan, 2018; Roman et al., 2018).

25.5.2 Nano-based formulation using plant-derived phytochemicals for biofilm inhibition

In scientific efforts to develop alternative therapeutic regimens against microbial infections and biofilms associated with drug resistance, we have received positive feedback to use phytochemicals in the fight against drug resistance patterns in ESKAPE pathogens. However, certain limitations such as lack of target-specific actions, poor solubility issues, and absence of long-term therapeutic effect hinder their applicability in clinical settings. Hence, it is imperative to use species-specific drug delivery platforms for improving drug therapeutics against microbial infections (Li et al., 2019; Subhaswaraj et al., 2020). In this regard, nanotechnological interventions owing to their unique physicochemical properties and biomedical applications could provide a new paradigm for target-specific delivery of putative phytochemical drug candidates for their improved therapeutic efficacy (Zhu et al., 2014). The nanotechnological interventions in drug development pipelines provide several advantages including the slow and sustained release of encapsulated drug moieties/phytochemicals, improved drug stability, increased therapeutic index, and more importantly prolonged therapeutic effect (Zaidi et al., 2017).

The presence of phytochemicals such as alkaloids, phenolics, saponins, tannins, terpenoids, etc., in plant extracts is considered as promising reducing and stabilizing agents in the green synthesis of nanoparticles. In this context, *N. sativa* seed extract was used as stabilizing and reducing agents for the synthesis of zinc oxide nanoparticles (ZnO NPs). The green synthesized ZnO NPs significantly attenuated the QS-mediated biofilm mechanics in *P. aeruginosa* and the foodborne pathogen, *Escherichia coli*. Thus, the developed ZnO NPs could be instrumental in the food packaging and food processing industries (Al-Shabib et al., 2016). The reducing ability of medicinal plant extracts was explored for

the synthesis of silver nanoparticles (AgNPs), which characteristically improved biofilm inhibition in pathogenic microorganisms, *P. aeruginosa* and *S. aureus* (Mohanta et al., 2020). The biocompatible chitosan nanoparticles also served as encapsulating agents for several phytochemicals and drug moieties. In this regard, bioactive phytochemicals, ferulic acid, and cinnamaldehyde were encapsulated onto chitosan nanoparticles. The encapsulated nanoparticles exhibited a promising response in mitigating QS-mediated virulence phenotypes production and also inhibited biofilm formation. It was also evident from the studies that phytochemicals-encapsulated nanoparticles have shown comparatively improved biological activities than that of nascent ferulic acid and cinnamaldehyde (Pattnaik, Barik, et al., 2018; Subhaswaraj et al., 2018). Later on, chrysin-loaded chitosan nanoparticles also critically improved the anti-biofilm potential of chrysin by concomitant decrease in the production of exopolysaccharides and biofilm formation in *S. aureus* (Siddhardha et al., 2020).

Earlier, baicalein-fabricated gold nanoparticles (BCL-AuNPs) significantly inhibited the QS-regulated virulence phenotypes (e.g., exopolysaccharides, swarming motility) in *P. aeruginosa* PAO1. The bioactive flavone, baicalein, thus served as a reducing and capping agent for the synthesis of gold nanoparticles. The results thus emphasized the use of phytochemicals-based nanomaterials for the treatment of biofilm-mediated chronic infections (Rajkumari et al., 2017). Using the bioactive components of different plant parts as reducing and capping agents, silver nanoparticles (AgNPs) were synthesized. The synthesized AgNPs exhibited promising biofilm inhibitory potential against MDR *P. aeruginosa* (Feizi et al., 2018; Habibipour et al., 2019; Singh et al., 2018). Recently, a polymer-stabilized carvacrol-in-water nanocomposite (NC) was designed and developed for effective therapeutic agents against *P. aeruginosa* biofilm. It was evident from earlier studies that the therapeutic index of phytochemicals critically improved after being used in a combination with nanocomposites by minimizing the MICs against pathogenic microorganisms (Landis et al., 2018; Li et al., 2019). Hence, the bioactive phytochemicals could be used in combination with suitable nanoplatforms not only to improve their therapeutic index but also to improve the localized and sustained release at the target sites for improved and long-term therapeutic effects.

25.6 Future perspectives

As discussed earlier, biofilm is the most predominant mode of ESKAPE pathogens to allow the growth of embedded bacterial communities from environmental stress including the stress of antimicrobial treatment. ESKAPE pathogens being active biofilm producers possess a significant challenge to our healthcare settings and current R&D sectors for antimicrobial therapeutics. In this context, it is imperative to quest for bioactive phytochemicals as promising alternatives to tackle the highly resilient biofilm dynamics. In recent years, phytochemicals are considered as potential agents to quench the pathophysiological factors responsible for biofilm development and drug resistance. Phytochemicals are being actively explored as QSIs, anti-biofilm agents. However, the majority of research works are still in preclinical settings, and more evidence-based scientific investigations need to be carried out for their ability to pass the clinical trials (Das et al., 2021). The emergence of advanced computational tools could provide novel avenues to develop suitable drug candidates from plant origin for their role in QS inhibition and mitigation of recalcitrant biofilm dynamics in ESKAPE pathogens (An et al., 2021; Chaieb et al., 2022). No doubt, computational approaches characteristically improved the screening of putative drug candidates for specific therapeutic applications, but the rate of molecules identified from *in silico* tools to introduction into the market remains very less. In this context, more sophisticated and advanced tools should be designed to improve the efficacy of such candidates in clinical settings.

Key points

Similarly, nanotechnological interventions also revolutionized the therapeutic index of nascent phytochemicals in the fight against chronic microbial infections. In addition, nanomaterial impregnations of anti-biofilm devices also critically improved our sincere efforts to challenge biofilm-associated infections. However, the use of nanotechnology-based efficacy is short term and environmentally toxic. Hence, it is imperative to develop regulatory bodies to address the issues associated with nanotechnological interventions in drug development pipelines (Ramasamy & Lee, 2016; Subhaswaraj et al., 2020). One more interesting aspect is to tackle biofilm-associated infections by using putative phytochemicals in combination with conventional antimicrobials for improving therapeutic efficacy. In addition, drug repurposing could be a viable alternative for the use of phytochemical drugs which were initially used for other therapeutics and could be intertwined with biofilm infections and drug resistance. In this context, more extensive research should be carried out with advanced computational and molecular tools for effective treatment regimens against chronic microbial infections and biofilm-mediated drug resistance in ESKAPE pathogens.

Acknowledgment

We would like to acknowledge OHEPEE, Govt. of Odisha, for providing financial support. The author, Subhaswaraj Pattnaik also acknowledges the Science and Engineering Board (SERB), Department of Science and Technology (DST), Govt. of India, for the award of National Post-Doctoral Fellowship (NPDF) (File Number: PDF/2021/001260).

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