JVMR. pISSN: 2357-0512 - eISSN: 2357-0520 Abdelaziz,2025. . 10.21608/jvmr.2025.383129.1131

Review Article

Current and Emerging Control Approaches of Biofilm Formation of Bacterial Pathogens

Sahar A. Abdelaziz * **and Fatma I. Mohamed**

Department of Hygiene, Zoonoses and Epidemiology, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef 62511, Egypt

abdelaziz.sahar@yahoo.com

Abstract

Biofilm is a recent prime driver that is challenging prospects for one health strategy. It is a major virulence characteristic linked to numerous significant global health issues and plays an integral role in multiple microbes' pathogenicity. One of the most common obstacles to biofilm formation is its profound relationship with chronic and recurrent infections. They also serve as genetic reservoirs and enhance environmental persistence. The ability of several bacterial species to adhere to numerous living or non-living surfaces and enclose themselves in a biofilm structure is closely linked to their ability to survive for extended periods outside of the host. The creation of biofilms increases resistance to the immune system, various physical stresses, and multiple chemicals, including disinfectants and antimicrobials. Moreover, biofilm production is frequently linked to significant financial losses and treatment failure. Likewise, a beneficial association between biofilms and escalating antibiotic resistance, which is linked to unsuccessful therapies and the rising fatality rates in the community, was observed. Therefore, several approaches, including bacteriophages, plant extracts, essential oils, enzymes, and nanoparticles, are among the most promising bioactive protocols exhibited auspicious efficacy with potent delivery platforms targeting sustained futures of a wide range of biofilm microbial infections.

Keywords: Bacteria, Biofilm, Chemical-Resistance, Control, Fatality, Virulence

Citation. Abdelaziz, S. A. and Mohamed, F. I. Current and Emerging Control Approaches of Biofilm Formation of Bacterial Pathogens. In Press. https://doi.org/10.21608/jvmr.2025.383129.1131.

Article History: **Received**: 08-May-2025 **Revised**: 27-Jun-2025 **Accepted**: 16-Aug-2025

1. Introduction

Bacteria, fungi, yeasts, and molds are examples of microorganisms that may aggregate and colonize both living and non-living surfaces in a dynamic process, forming a single matrix of extracellular polymeric substance (EPS) that is known as a biofilm (**Haaber et al. 2012**). Van Leeuwenhoek was recognized for the discovery of microbial biofilms after observing bacterial colonies on tooth surfaces using a simple microscope. Also, Heukelekian and Heller's 1940 denoted the "bottle effect" of marine microbes and examined the existence of surfaces that these organisms adhere to and associated with significant bacterial activity and growth (**Percival et al., 2011**). Proteins, polysaccharides, teichoic acids, phospholipids, and other polymers are the main constitutes of the extracellular polymer substance (EPS), which are permanently attached to a surface (**Chmielewski and Frank, 2003**). Additionally, A 1 gram biofilm contains around 10^8 and 10^{11} cells. Each microbial pathogen can adhere to objects in a distinctive manner. Among the mechanisms are pili, flagella, proteins, and polysaccharide adhesions (**Hall-Stoodley and Stoodley, 2002**). The biofilm cycle comprises six phases: the initial reversible contact, followed by bacterial adhesion and aggregation, microcolony formation, maturation, quorum sensing, and dissemination (**Flemming et al., 2016**) (Figure 1).

2. Biofilm Cycle

2.1. Initial Reversible Contact

This process begins next to surface contact by a planktonic cell: bacteria adhere to the substratum via the cell pole or flagellum, followed by longitudinal attachment. The physical and chemical characteristics of the bacterial cell and its surroundings can have an important effect on the initial adhesion process of bacteria (**Gupta et al., 2016; Veerachamy et al., 2014**). Furthermore, *Salmonella* serovar, surface, nutritional sources, temperature, and pH are some of the other variables that affect the extremely challenging procedure that results in cellular attachment (**Roy et al., 2021**).

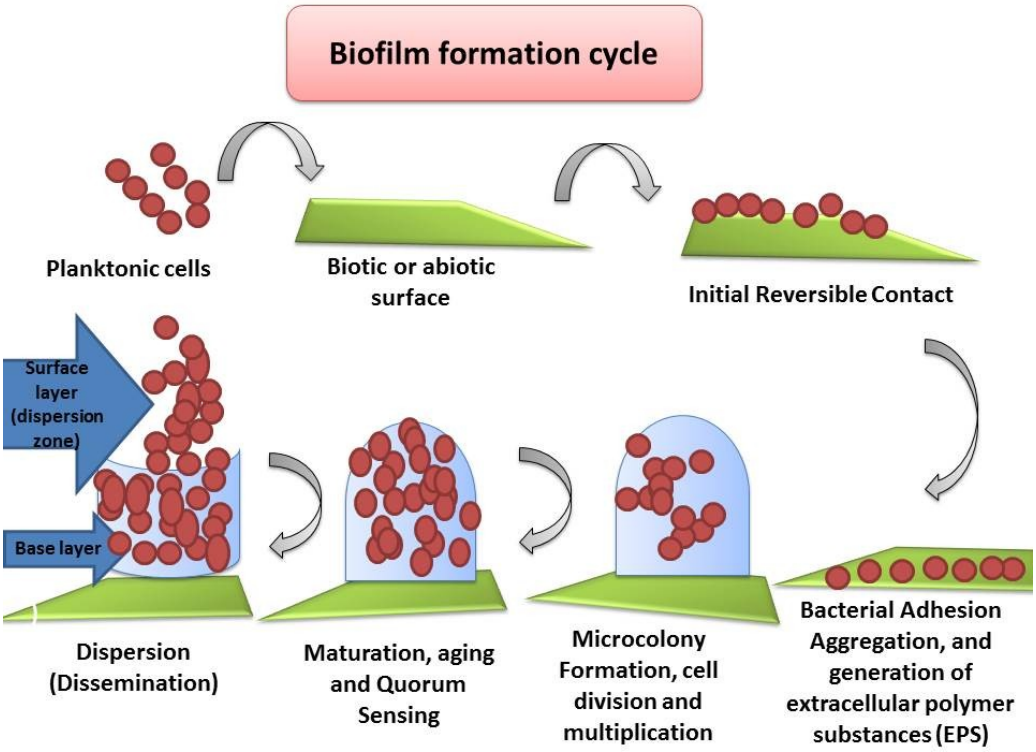

Figure 1: Stages of biofilm formation

2.2. Bacterial Adhesion and Aggregation

Adhesion and aggregation are known as the anchoring or latching phase. At this point, the adhesion process hardens the loosely attached organisms through the generation of extracellular polymer substances (EPS) that interact with substrates and/or receptor-specific ligands found on fibrillae, fimbriae, and pili, or both (**Flemming et al., 2016**). As a result, the organisms are better able to remain attached to the surface to whom they are connected.

At this stage, the organism will have clustered on the exterior surfaces stably and irreversibly, and the adhesion will have become irreversible in the absence of any kind of physical or chemical interference. In addition, certain microbial pathogens can attach and various surface-conjugated organisms, resulting in surface aggregation. Each bacterium creates different adhesions, and some of these adhesins are transcriptionally regulated. This enables organisms to change from a sessile to a planktonic state in response to environmental stressors (**McKenney et al.,1998; Mack et al., 1996**).

2.3. Microcolony Formation

Following bacterial attachment, cell division and multiplication create microcolonies. Microcolonies are the fundamental structural elements of a biofilm. They are rod-shaped and comprise 10.0-25.0% cells and 79.0-90.0% extracellular polysaccharides (EPS), which are mostly proteins, polysaccharides, and extracellular DNA (eDNA) (**Stoodley, 2016**). Additionally, this process is initiated by certain chemical signals in extracellular polymeric substances (EPS) and microcommunities (**McKenney et al., 1998**). Bacterial colonies usually have a range of microcommunities in their biofilm structures that can work together to facilitate the passage of water and significant metabolites as well as the removal of debris.

2.4. Maturation

The adhering tiny colonies develop into an aged biofilm with a distinctive three-dimensional structure at this stage. Connected cells continue to grow and mature at this phase (**Zhao et al., 2017**). The associated bacterial cells can release signaling molecules that facilitate maturation and cause the expression of biofilm-related determinants. Signaling molecules increase the bacterial pathogenicity via modifying gene expression. The process starts off with the expulsion of EPS from the microbial cells, which strengthens the framework of the biofilm and protects it from antimicrobial substances (**Gupta et al., 2016**).

2.5. Quorum Sensing (QS)

QS is the method by which cell-to-cell communication is an essential process by which bacterial populations synchronize their actions and establish highly populated communities within biofilms (**Hawver et al., 2016**). This process entails the synthesis and identification of signaling molecules, specifically N-acyl homoserine lactone (AHL), in Gram-negative bacteria. Once AHL concentrations surpass a certain threshold, they stimulate certain receptors, resulting in modified gene expression and the commencement of quorum-sensing-regulated pathways (**Ivanova et al., 2013**). Quorum sensing controls multiple elements of biofilm formation, such as the production of extracellular polysaccharides like pel and PSL, which have a role in maintaining the structural stability of the biofilm (**Colvin et al., 2011**). Moreover, by boosting the exchange of nutrients and encouraging the formation of protective proteins and polysaccharides within the biofilm, it allows bacterial communities to endure unfavorable circumstances like exposure to antibiotics and drying out (**Xu et al., 2024**).

2.6. Dispersion (Dissemination)

This stage, which is crucial for the development of biofilms, allows the bacteria to move from one area of an infected body to another to disseminate the disease condition. This stage is generally referred to as metastatic implantation **(Chao et al., 2014**). The biofilm comprises two distinct layers (**Veerachamy et al., 2014**). One layer is the base layer, where the bacteria are present in greater quantities, while another layer, called the surface layer, serves as a dispersion zone where the bacteria dissipate and persist in their environment. This stage causes chronic infection and other serious disorders, such as embolism, requiring immediate medical intervention. In this stage, the important nutritive materials become limited and release stressful products and waste outcomes linked to the dispersal of the microbial cells to adjacent regions in the victim body or elsewhere of the medical implant areas (**Oppenheimer-Shaanan et al. 2013**). The dispersion process commences when either single cells or cell aggregates begin to separate from the biofilm (**Gupta et al., 2016**), as well as the gene regulation routes that are associated with the decomposition of EPS. Among these methods is the production of enzymes by the microbial cells that facilitate the breaking down of saccharides. By dissolving the polysaccharide framework that retains the biofilm in place, this procedure releases the outermost layer of the bacteria (**Grande et al., 2014**). After being released, the bacteria either establish secondary biofilms in other bodily organs or float freely on the surface by inducing the synthesis of proteins which promote motility (**Gupta et al., 2018; Xu et al., 2019**).

3. Factors Affecting Biofilm Formation

According to **Puttamreddy et al. (2010)**, the biofilm development process is dynamic and intricate, involving the initial adherence of bacterial cells to the substrate, physiological alterations inside the microbe, the proliferation of adherent cells to create microcolonies, and the ultimate stage of biofilm maturity. These environmental elements, including temperature, pH, ionic strength, and nutrition content, might affect the transition from a planktonic to a sessile phenotype (**Agarwal et al. 2011**).

The pathogen type, the presence or absence of other bacterial traits, extracellular polymeric materials, cell adhesion molecules, and environmental parameters (such as temperature, pH, salt, relative humidity, oxygen availability, and nutrition) all have an impact on the development of biofilms (**Alotaibi et al., 2021**). Moreover, increased antibiotic resistance and the presence of bacterial biofilms are strongly correlated with antibiotic resistance. Currently, antibiotics are the primary tool used to prevent and treat *Salmonella*. Nevertheless, the widespread use of antibiotics in clinical, veterinary, and animal-derived food processing is increasing the risk of drug resistance to *Salmonella*, and multidrug resistance (MDR) is also increasing. Therefore, it is crucial to monitor its drug resistance data to analyze the evolution of its drug resistance spectrum, guide therapeutic therapy, and prevent the predominance of *Salmonella* infection **(Zhang et al., 2020)**.

Bacterial resistance to antibiotics is seriously threatening public health. Various *Salmonella* serotypes exhibit a comparatively high level of antibiotic resistance **(Mayrhofer et al., 2004**). The problem of antibiotic resistance becomes more serious when the biofilm formation ability of these bacteria is also considered.

4. Approaches for Biofilm Prevention

Unfortunately, no method can effectively stop or manage undesirable biofilm growth without adverse consequences. Cleaning and disinfecting surfaces before bacteria firmly adhere to them are the primary methods of preventing biofilm development (**Simoes et al., 2006**). Although the cleaning procedure can eliminate ≥90% of surface-associated bacteria, it cannot be used to eradicate them. (**Gramme et al., 2007**). Additionally, biofilm detectors have already been developed to track bacterial surface colonization and enable biofilm management throughout the initial stages of growth (**Pereira et al., 2008**). A mechatronic surface sensor that can identify biofilms in their early stages of formation (**Pereira et al., 2008**). Additionally, this sensor could determine when a surface had been chemically and biologically cleaned, evaluate the level of cleaning, and detect the presence of cleaning agents on the surface (**Pereira et al., 2009**) (Figure 2 & Table 1).

4.1. Physical Methods

Salmonella biofilms have been treated using various physical techniques, including irradiation, plasma, electric or magnetic fields, and ultrasonic power (**Liu et al., 2022**). These techniques can either encourage or inhibit the production of biofilms by separating the biofilms from contact surfaces, deactivating the microbial cells inside the biofilms, and causing damage to the biofilm structures and microbial DNA (**Yu et al., 2020; Gilmore et al., 2018; Jung et al., 2018**). Although physical solutions show great promise for controlling biofilms, their effectiveness may not be sufficient to inactivate mature biofilms completely.

4.2. Chemical Methods

Environmental factors and the age of the biofilm may be the most significant factors affecting the resistance of *Salmonella* biofilm cells. When *Salmonella* biofilms are exposed to disinfectants at concentrations below the minimum inhibitory concentration (MIC), they may develop an adaptive stress response that increases their resistance and cross-resistance capabilities. To manage biofilms, innovative antibiofilm techniques are necessary, considering these challenges. Several novel strategies, such as the use of natural materials (plant extracts and essential oils) (**Pompilio et al., 2023; Rossi et al., 2022**), enzymes, nanoparticles, bacteriophages, and physical treatments, are successful in breaking down *Salmonella* biofilms. *Salmonella* biofilms can be targeted by synergistically combining these several antibiofilm strategies.

4.3. Bacteriophages

Bacterial bacteriophages, which are groups of viruses that attack and multiply within bacterial cells, have been employed to fight biofilms (**Simmons et al., 2018**). Because these viruses precisely target and kill bacteria, they pose no threat to people, animals, or even the environment (**Endersen and Coffey, 2020; Simmons et al., 2018**). As a result, phages are useful and natural tools against microbial biofilms that may be used in food storage, biological control, and treatment (**Pires et al., 2017**). Combining different phages is another efficient antibiofilm technique. Several phage strains were amplified independently by **Ornellas et al. (2017)** and then merged in a 1:1:1 ratio known as a phage pool. After 9 hours of treatment in the phage pool, it was found that *Salmonella* biofilms that had previously developed on adherent glass started to dissolve.

Comparably, **Islam et al. (2019)** developed a phage cocktail comprising three phages (LPST153, LPSTLL, and LPST94) and observed that the phage cocktail inhibited *S.* Typhimurium biofilms formed on a 96-well microplate by 44.0–63.0% and decreased them by 5.2–6.4 log on a *Salmonella Shigella* agar surface. The limited lytic range of phages restricts their use; hence, combining phages with other antibacterial compounds is a successful strategy (**Jiang et al., 2021; Yüksel et al., 2018**).

4.4. Plant extracts

Applying plant extracts to eradicate and eliminate biofilms has gained more attention lately (**Sadekuzzaman and Ha, 2015**). The inclusion of bioactive substances, such as phenolic compounds, certain oligosaccharides, flavonoids, and lipids, such as terpenes and fatty acids, provides plant extracts with their antibiofilm properties (**Pompilio et al., 2023**). These bioactive chemicals primarily prevent or eradicate biofilms by preventing polymeric matrix formation, adhesion between cells, and attachment, stopping the synthesis of an extracellular matrix, and disrupt-

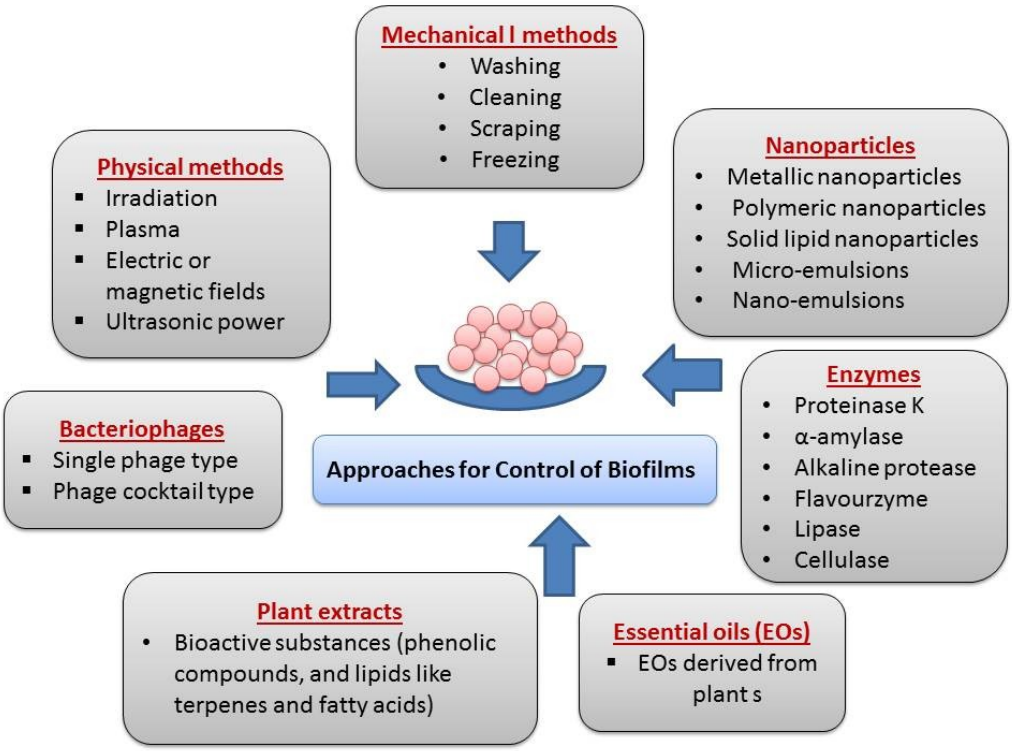

Figure 2: The common approaches of biofilm formation

ing QS signaling (**Lu et al., 2019**). Moreover, **Selim et al. (2022)** investigated the high potency of *Salvia officinalis* leaves EOs against biofilm development, and they indicated that biofilms formed by *S.* enterica were efficiently removed after 1 h at 5.0%. Also, **Liu et al. (2022)** investigated the role of clove EOs in biofilm formation, which inhibited by 90.29% at 1/8 MIC and clarified that clove EOs can inhibit metabolic activity and EPS production caused by *S.* Derby. **Sadekuzzaman et al. (2018)** denoted the efficacy of Tea tree EOs against strains of S. Enteritidis and reported their evidence in decreasing values of biofilms 2.3 log CFU/cm2 at MIC values. Furthermore, **Liu et al. (2017)** emphasized the role of the polyphenolic extract of olive leaf EOs in suppressing the biofilm formation of *S.* Enteritidis at 74.0% at 1/4 MIC.

4.5. Essential oils

The antibacterial properties of essential oils (EOs), which are secondary metabolites produced by volatile and medicinal herbs, make them a viable and sustainable component in various biological control sectors (**Falleh et al., 2019**). Since the chemical component function of most EOs as antimicrobial substances targets both floating and attached cells, there has been an upsurge in interest regarding their anti-biofilm issues (**Rossi et al., 2022**). EOs decrease or eliminate existing biofilms in addition to preventing the production of new ones (**Wang et al. 2017**). Although the use of EOs alone to treat biofilms was successful, the outcomes were greater when EOs were combined with other antibiotics. Also, **Tokam Kuate et al. (2021)** noticed that both an aminoglycoside antibiotic and thymol interacted harmoniously to hinder the development of biofilms by 43.0% and to eradicate preexisting biofilms by 40.0%, exhibiting no antagonistic consequences.

4.6. Enzymes

According to **Rudolph et al. (2018)**, enzymes are regarded as "green chemicals" as they are entirely biodegradable and do not adapt or become resistant to several pathogens. Enzymes may be able to strike and soften the matrix made up of EPS in the biofilm , thereby weakening the matrix's physical stability and causing the cells to separate from the biofilm structures (**Kim et al., 2019**). Consequently, one other approach to successfully managing issues related to biofilm contamination in the food industry is the development of enzyme-related therapy.

A study investigated by **Liaqat et al. (2021)** denoted the capabilities of proteinase K enzymes as an antibiofilm approach against *S.* Gallinarum

Table 1: Examples for the common approaches of biofilm control

Chemicals used	Treatment strategies	Target bacteria	Mode of action	Advantages	References
Natural chemicals	Cinnamaldehyde	*S.* Typhimurium	Peroxiredoxin, ATP synthase alpha chain protein, conjugal transfer nickase/helicase *TraI* and elongation factor G metabolic activity	Inhibiting biofilm formation and eradicating pre-formed biofilm	**Albano et al., 2019**
	Baicalin	*P. aeruginosa*	*LuxS*, *brpA*, *ffh*, *recA*, *nth* genes encoding virulence factors, adhesion proteins, and proteinases QS-regulatory genes	Reduce the aggregation of *P. aeruginosa* and biofilm formation	**Luo et al., 2017**
Combination therapy	Essential oils	Multidrug resistant *Staphylococcus*	Inhibit the formation of biofilm, and inhibit the growth and reproduction WalK/R system	Destroy the biofilm growth	**Rosato et al., 2020**
	Tobramycin and cuminaldehyde	*P. aeruginosa*	ROS and membrane permeability of bacterial cell	Promote biofilm dispersal and improve drug utilization	**Chatterjee et al.,2023**
Bacteriophage and phage enzymes	Vancomycin-phage EFLK1	vancomycin-resistant *Enterococcus faecalis*	Increase bacterial sensitivity to antibiotics	Treating bacteria within the biofilm matrix and biofilm eradication	**Shlezinger et al., 2019**
	T7Ag-XII phages armed with AgNPs	*P. aeruginosa* and *E. coli*	Quorum sensing	Inhibition of biofilm formation	**Pei and Lamas-Samanamud, 2014**
Nanomaterials based drug delivery system	Liposomes cationic peptide conjugated liposomes	*S. aureus*, *E. coli* and *P. aeruginosa*	*IcaB* gene	Anti-biofilm and anti-inflammatory activity, Enhance biofilm inhibition and clearance rates, and improve drug utilization	**Hemmingse et al., 2023**

isolates recovered from broiler chickens, which could prevent 80.0% of biofilm formation. Moreover, using the proteinase K enzyme not only prevents biofilm formation but also breaks down the immature biofilm matrix, as shown by **Kim et al. (2019)**. However, because of the intricate EPS matrix, it may be challenging for enzymes to break down mature biofilms on their own. As a result, the disinfectant and enzyme combinations performed more effectively than either therapy alone. When added to food, flavourzyme, a commercial peptidase with antioxidant benefits, inhibits food from deteriorating and has antibiofilm characteristics.

In addition to demonstrating Quorum Quenching (QQ) action, flavourzyme markedly reduced the overall expression ranges of the virulence-related genes (*rpoS*, *rpoH*, *hilA*, *spvR*, *avrA*) and QS (*luxS*) of *S.* Typhimurium. *Salmonella* biofilms have been shown to respond well to the application of combination of several enzymes. A combination of α-amylase and alkaline protease was able to eliminate 93.0% and 96.0% of *Salmonella* biofilms that had developed on *Salmonella Shigella* agar surfaces (**Iniguez Moreno et al., 2021**). Similarly, a combination of amylase, lipase , and protease could remove approximately 2.3 log CFU/cm^2 of *S.* Typhimurium biofilm cells on *Salmonella Shigella* agar (**Ripolles Avila et al., 2019**). Furthermore, the use of an extracellular enzyme mixture, such as cellulase, protease and amylase, generated by the EU2D-21 mutant of *Penicillium janthinellum* showed a potent ability to treat *S. enterica* biofilms after 1 h at 50°C, and this extracellular enzyme eliminated approximately 80.0% of the biofilm framework (**Nagraj and Gokhale, 2018**).

4.7. Nanoparticles

The ability of nanoparticles (NPs) to transport pharmaceutical drugs to the targeted location in optimum dosages, inhibit their suppression, and increase the therapeutic effect of their treatment with fewer adverse reactions has drawn attention most recently due to their possible medical use (**Wang et al., 2020**). Nano formulations may pass through biological barriers, including biofilms, and selectively target bacteria specifically as opposed to other cells via their small dimensions, extensive surface area, and extreme sensitivity (**Blanco et al., 2015**). Additionally, NPs remain in the blood for an extended period after they immediately leave the body via the kidneys. The majority of research has primarily been done *in-vitro*, even though NPs are becoming increasingly successful as antimicrobials. However, relatively little clinical research has been emerged. To ensure that the prevalent antimicrobial and anti-biofilm evidence of NPs with the fewest potential adverse effects, clinical applications must take into account, the physical and chemical characteristics, dosage, biocompatibility, as well as toxic relationships of those materials (**Mohanta et al., 2023**).

Zinc oxide (ZnO), which has the benefits of stability, non-toxicity, and relative safety, is one of the metals and their oxides that can withstand the challenging circumstances of the environment (**Kakati et al., 2020**). Nanomaterials made from these metallic oxides have many applications, including antibacterial and antidiabetic properties as well as use in waste remediation, energy, and agriculture (**Kumar et al., 2022**). Zinc oxide nanoparticles have demonstrated dose-related antibiofilm characteristics against biofilms formed by food-borne pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus enterica*. Ideally, the majority of biofilm inhibitory medications should change the structural and physicochemical characteristics of bacteria, such as cell motility, phagocytosis, surface adhesion, and reactive oxygen species (ROS) production, rather than killing the cells.

Additionally, silver (Ag) eliminates biofilms and exerts remarkable bactericidal effects on a broad range of microbial species. AgNPs have more antibacterial activity than antibiotics and are often used as antimicrobial medications. Additionally, they are used in clinically manufactured dressings for wounds, implants, and catheters (**Fulaz et al., 2019**). Furthermore, AgNPs demonstrated a low degree of toxicity when applied in the *in-vivo* approaches that was well tolerated at a moderate dosage (**Hussain et al., 2019**). To reduce the adverse effects of NPs, AgNPs should be properly bonded to suitable biomaterial surfaces (**Taglietti et al., 2014**). However, by inhibiting aggregation, decreasing cellular absorption and cytotoxicity, and improving site-selective delivery, AgNPs modified with other polymers, metals, or antibiotics can become more successful in the control of biofilm formation (**Liu et al., 2017**). Also, AgNPs encapsulated in poly (caprolactone) and coated with chitosan (**Permana et al., 2021**) to be less harmful and more effective in eliminating various diseases.

Gold nanoparticles (AuNPs) are more effective at preventing biofilm formation than AgNPs. This is because AuNPs lower the hydrophobicity index and exo-polysaccharide synthesis (**Rajkumari et al., 2017**). It is believed that AuNPs' antibacterial action involves disrupting ATPase production and breaking down bacterial membranes. Furthermore, nicotinamide becomes targeted, the bacterial respiratory chain is affected, and the ribosomal subunit's capacity to bind to tRNA is blocked (**Baptista et al., 2018**). Likewise, AuNPs may have little effect on biofilms if they do not significantly affect cell growth, and their capacity to inhibit biofilm formation is dose-dependent (**Ali et al., 2020**). The antibacterial properties of AuNPs may be enhanced by mixing them with antibiotics.

Numerous applications of nanotechnology are available for the prevention, control, and treatment of several diseases. These techniques involve mixing pharmaceuticals and biomolecules with polymers or devices, offering benefits including gradual and regulated release of drugs, enhancing penetration into tissue with extreme efficiency, and increased protection from drug breakdown (**Lin et al., 2015**). Currently, the most common nanosystem forms for the delivery of biologically active substances (MNPs) include metallic nanoparticles, polymeric nanoparticles (PNs), solid lipid nanoparticles (SLNs), micro-emulsions (MEs), and nanoemulsions.

Drug delivery systems that utilize nanotechnology can enable the direct interaction of medications with the complex architecture of biofilms while functioning at different stages of the biofilm growth process, increasing the potential useful-

ness in biofilm therapy. The biofilm polymer matrix can be directly affected by nanoemulsions, LIPs, SLNs, and lipoproteins, which can increase nanoparticle fusion and cause bilayer-lipid fusion and protein denaturation. This facilitates interaction with the microbial cells and allows the nanoparticles to infiltrate the biofilm more easily (**Forier et al., 2014**).

Compared to cationic nanoparticles, such as polystyrene and gold nanoparticles, anionic nanoparticles have a substantially lower degree of toxicity (**De Jong et al., 2008**). Cationic nanoparticles have been demonstrated to cause coagulation and haemolysis. Also, skin, respiratory system, parenteral administration, and other routes are some of the ways that nanomaterials can enter the body. They are going to combine with the plasma proteins in the blood circulation, and most likely leading to the formation of a protein corona that is linked to several grades of toxicities caused by elevated ROS levels and disturbances in the homeostasis of the body (**Khanna et al., 2015**). also, oxidative stress and DNA damage might result from ROS, which would subsequently promote the formation of micronuclei. Additionally, the ability of macrophages to absorb silver nanoparticles, regardless of their size, will probably increase the production of inflammation-related mediator,s including IL-1, TNF-α, and MIP-2 (**Albanese et al., 2012**). Investigating the precise processes that control how such particles are eliminated from the body is crucial since nanoparticles tend to accumulate in the liver (**Parveen et al., 2012**). Furthermore, it is uncertain how long nanomaterials will stay in the environmental settings as well as what their long-term impacts (**Khan et al., 2021**).

4.8. Limits of Nanoparticle Applications

Over the past decade, the application of nanoparticles (NPs) has been commonly associated with toxicity issues in humans or animals. Furthermore, the harmful effects of NPs differed according to the application method. Cell death is frequently linked to the penetration of titanium dioxide Nps through the skin, follicular cells, and sweat glands **(Tak et al., 2015)**. Furthermore, the inhaled NPs reach the lungs directly, pierce the epithelial layer, and cause lung cancer by penetrating the surrounding lymph node **(Missaou et al., 2018)**. Furthermore, the frequent use of silver oxide and aluminium oxide nanoparticles is causing lung cancer, where NPs can spread throughout the body and lodge **(Oberdörster et al., 2005)**. The application rate from the capillaries into the target organs is also influenced by the physicochemical characteristics of the NPs being employed **(Yang et al., 2007)**.

Liver damage is commonly induced as a result of the penetration of metal ions of silver NPs into liver cells **(Wang et al., 2017)**. NPs are frequently linked to the buildup of gold molecules in the liver and the activation of hepatic macrophage-induced liver damage **(Bartneck et al. 2012)**. Additionally, nephrotoxicity results from the tiny molecules of NPs being filtered by the kidney **(Missaoui et al., 2018)**. Although the impermeability of the blood-brain barrier (BBB) prevents most NPs from entering the brain **(Hoet et al., 3005)**, a small number of NPs, such as silver, titanium dioxide, and zinc oxide NPs, can cause oxidative stress in the brain by passively diffusing over the BBB or by being endocytosed by receptors **(Sharma and Sharma, 2007)**.

5. Conclusion

Effective therapies and management techniques for microbial infections caused by biofilms are hampered by several difficult issues. Likewise, assessing the effectiveness of new drugs for treating biofilm infections is hampered by the difficulty of detecting and tracing back the source and the expense of treating illnesses caused by biofilms. Thus, the approach of drug delivery using natural products, sustainable eco-friendly practices, and nanotechnology may be employed in the near future for treating and avoiding microbial biofilms in both *in-vitro* and *in-vivo* research.

Moreover, the potential of combining multiple technologies, integrating two or more distinct control technologies, is intriguing. Also, it provides promise for novel approaches to prevent or manage the development of harmful biofilms, enabling more effective use of therapeutically available medications with negligible effects on the one health approach. Furthermore, a number of strategies are nonetheless in their development and have not yet finished clinical trials or entered the commercial market, while being important research topics.

6. Future Prospects

It is essential to conduct comprehensive investigations of all control strategies, especially those involving nanoparticles, over extended periods, focusing on biofilm dynamics, host reactions, the mode of action on various bacterial cell organelles, and the capacity of tested chemicals to identify persistent problems in living hosts without posing cytotoxic risks.

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Article Information

Ethical Approval. Not applicable.

Funding. The research received no external funding.

Conflict of Interest. The authors declare no conflict of interest.