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Review: **Biofilms Formation by Pathogenic Bacteria**

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ABSTRACT : Biofilm is a complex structure specific for microbial communities formed on biotic and nonliving surfaces such as prosthetic or artificial teeth ; increase their resistance to stressed conditions and protect themselves. Biofilm surrounding bacterial cell colony had increased their resistance to antibiotics. Several microorganisms able to form biofilms on adherent surface such as Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli and Bacillus cereus. Bacillus cereus is a Gram positive, rod-shaped bacteria, found in soil but it is also isolated from plant roots and food products. Some B. cereus strains are foodborne pathogens responsible for two types of gastrointestinal diseases, diarrhea and emesis, caused by distinct toxins. Disruption of biofilm forming may be better than removing them after formation. Several strategies were used to overcome biofilm such as nanoparticles, antibiotics and chemical treatment. In this review, microbial biofilms in several fields as food industry and medicine are highlighted and illustrate the methods which are used to break down biofilm.
Keywords: *Biofilm; Food; Antibiotics.*

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I. INTRODUCTION

In the 17th century, Antonie van Leeuwenhoek first observed animalcules on his own teeth. In 1940, the bottle effect was observed in marine microorganisms. This indicated that bacteria grow more often on the surface. In 1943, Zobell found that bacteria on surfaces were greater in number compared with the surrounding seawater and defined it as biofilm [1,2]. Biofilm originated as a defense mechanism for prokaryotes against too harsh conditions, it has garnered a lot of interest due to higher effect to public health, medicine, food and pharmaceutical industry. Structured groups of microbial cells attached together and collapsed in an extracellular matrix with different density and composition were defined as biofilms [3]. Biofilm considered as adaption mode which enable microbial cell to survive in hard conditions such as UV radiation, sudden changes in pH values and draining [4]. This review summarizes the problems resulted from biofilm formation in food, medicine. Also, steps of biofilm formation and prevention of biofilm are highlighted.

II. Interaction of biofilm in food industry

In food processing, biofilms are the major cause of bacterial accumulation on food surfaces such as equipment and utensils, so that it is considered as a continuous source of food contamination [5,6]. Most of the pathogenic or spoilage bacteria in food production systems can be detected on surfaces in the form of planktonic or attached cells, or in community arrangements as a biofilm [7]. The ability of Staphylococcus aureus and Listeria monocytogenes to adhere on the surfaces of food contact materials including stainless steel, polypropylene, rubber, and glass, as well as on the surface of food products [8]. Heat-treated foods may be contaminated by many types of bacteria mainly spore-forming bacteria because of its ability to live with high temperatures and biofilm

forming on a living or abiotic surfaces [9]. Formation of microbial biofilms on the internal surface of thermal equipment such as sterilizers and pasteurizers may lead to corrosion of the material and to reduced efficiency of heat exchangers, these causing huge losses for the food industry [10].

In the food industry, factors such as temperature, pH of food materials, and availability of their residues highly affect the biofilm formation of pathogenic and spoilage bacteria. These factors may also increase the resistance of attached cells to disinfection procedures which make biofilm difficultly eliminated by normal cleaning procedures [11,12].

III. Interaction of biofilm in medicine

Bacterial biofilms are one of the key factors in chronic infections on the basis of higher tolerance to antibiotics and disinfectants; they can attack phagocytosis and immune system, two-thirds of bacterial infections in humans involve biofilms which display antimicrobial tolerance, and immune response evasions[13,14]. Biofilms often formed on the inert surfaces of implanted devices such as catheters, prosthetic cardiac valves and intrauterine devices, infections associated with the use of medical devices are difficultly treated [15,16]. Biofilm mostly threat public health due to antibiotics resistant nature and disease associated with indwelling medical devices [17,18]. When bacteria exist in a biofilm form, they become less susceptible to antibiotics, biofilm communities can be up to 1000-times more resistant to be removed than planktonic cells due to metabolic changes to cells and influencing drug permeability structural features [19].

Mechanism of bacterial resistance to antibiotics

1- Bacteria can modify itself to change the target structure for the antibiotic ex; fluoroquinolone antibiotics target DNA gyrase in Gram-negative cells, and mutation of the target site decrease drug binding and increase resistance [20].
2- Bacteria produce enzymes which can inactivate antibiotic and become ineffective such as Extended spectrum β-lactamases (ESBLs) include CTXM enzymes found in Gram-negative species reducing the efficacy of cephalosporins, aztreonam and penicillin [21].
3- Bacteria can prevent access of the antibiotics to target site by up-regulating the normal level of efflux activity of the cell or reducing the permeability of the cell membrane by repressing porin production ex; Acr AB-TolC in *E. Coli* or MexAB- OprM efflux pumps in *Pseudomonas aeruginosa* and able to export multiple drugs [22].

III. Steps of biofilm formation and factors affecting them

Basic structural units of a biofilm are microcolonies, which are rod shaped through which water flow [23]. Microcolonies consist of 10–25% of cells and 79–90% of extracellular polysaccharides (EPS)which mainly composed of polysaccharides, extracellular DNA (eDNA) and proteins [24].

Many factors can stimulate complex biofilm formation ex; some regulators, such as second messengers, c-di-GMP. The second messenger c-di-GMP was universally known as a switch molecule that intermediate the bacterial transition between a planktonic lifestyle and biofilm formation [25]. It is played an important role in the post-translational activation of exopolysaccharide biosynthesis [26]. Biofilm formation is directly proportional to c-di-GMP, high c-di-GMP levels induce biofilm formation yet, low c-di-GMP levels induce planktonic growth [27,28].

General biological model of biofilm growth cycle includes many steps.

First step called adhesion stage, at which cells attach to a surface by the weak van der Waals forces and hydrophobic effects [29,30]; in the sessile growth stage (second stage), a group of these cells forms microcolonies. The two steps are reversible steps because the cells attach together but can detach and return to a planktonic state [31]. Generally, attachment of microbial cells on surface can be modulated by physical properties, such as electrostatic charges, hydrophobicity, roughness and material of the surface such as rubber, stainless steel, polypropylene, and silicon [32]. After attachment, the biofilm forms through accumulation of bacterial cells via intercellular adhesion mechanism which occur via two primary mechanisms: polysaccharide and protein-dependent. The biofilm polysaccharide, poly-N-acetylglucosamine (PNAG, also called polysaccharide intercellular adhesin, PIA), is produced by the biosynthetic enzymes of the ica ADBC operon [33]. In third step of biofilm formation, cells are attached within a thick and stable complex biomolecular layer so that it is irreversible stage [34]. The complete matured biofilm matched a three-dimensional tower structure. After a biofilm is completely developed, cells dispersion occurs via both active and mechanical processes. These processes occur in the fourth stage (dispersal stage). The cells within the biofilm secrete disruptive factors, including phenol-soluble modulins, proteases, regulators and nucleases as well as cell–cell-adhesive matrix components [35].

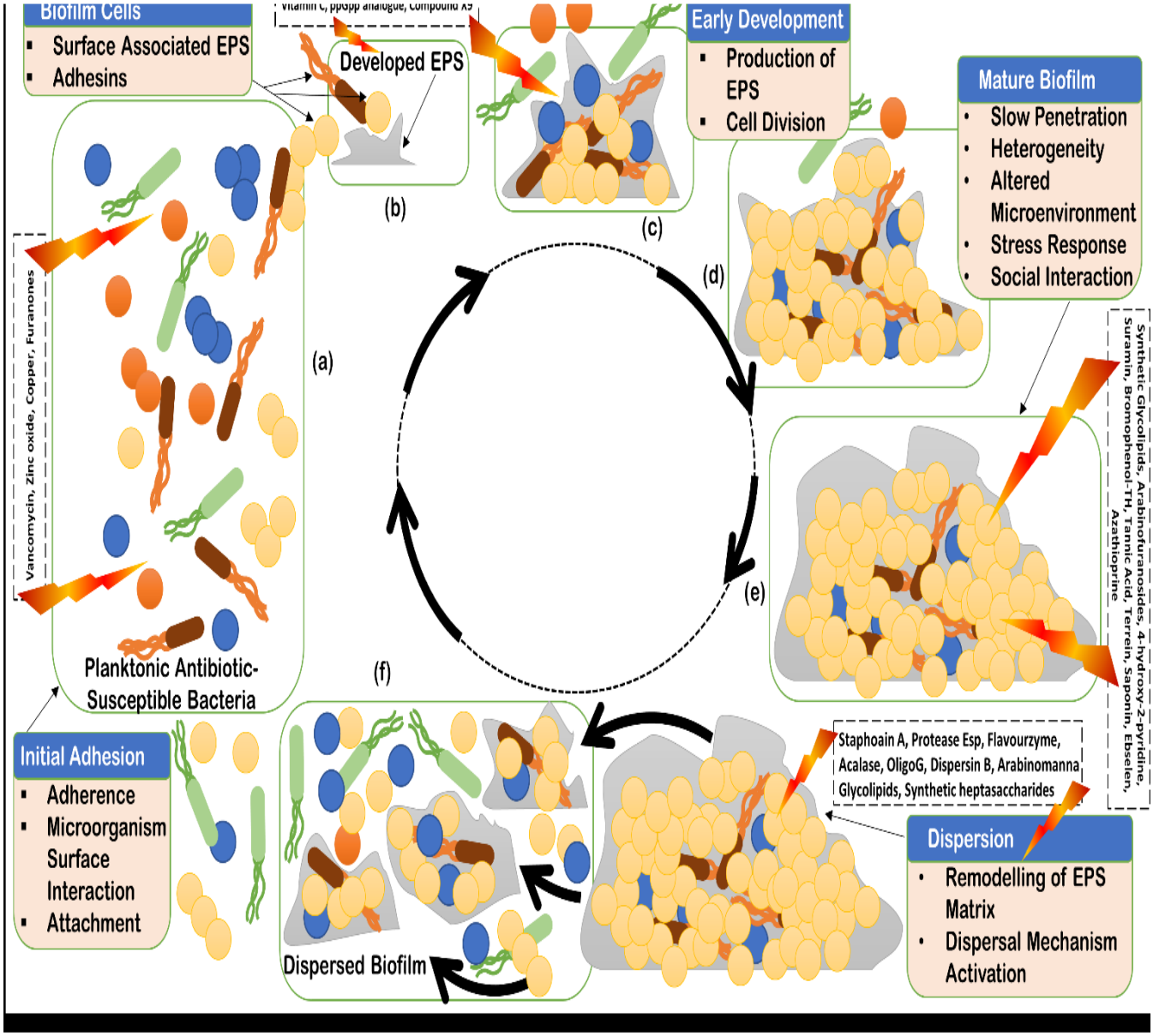

Figure 1. Stages of biofilm life cycle: initial adhesion **(a)**; initial developed extracellular polymeric substances (EPS) **(b);** early development of EPS production **(c);** further development of biofilm EPS for maturation **(d);** mature biofilm **(e);** and dispersion of biofilm **(f)** [36].

IV. Some bacterial biofilm producers

Biofilms were classified as the most common clinical barrier of the century according to Centres of Diseases Control [37]. Several types of bacteria can exist in biofilm form.

Staphylococci can attach to different surfaces, including abiotic material and human tissues as skin [38]. Also, S. epidermidis adhere to abiotic surfaces and form biofilms and cause large number of device-related infections [39]. Both *S. aureus* and *S. epidermidis* express a large number of microbial surface component recognizing adhesive matrix molecules (MSCRAMM) adhesion proteins that mediate adherence to host extracellular matrix proteins [40]. The stratum corneum of AD skin has increased fibronectin than healthy control skin, and *S. aureus* fibronectin-binding protein (FnBP) A and B can interact with fibronectin in human skin, *S. aureus* MSCRAMM clumping factor B (ClfB) that binds to fibrinogen and EPS proteins was important in biofilm formation under calcium-depleted conditions [41]. Morever, bacterial surface proteins directly attached to each other to allow *staphylococcal* cells to adhere together in the biofilm such as accumulation-associated protein (Aap)

of S. epidermidis that terminates in an LPXTG sortase that is covalently attached to the peptidoglycan of cell wall [42].

E. coli responsible for a wide range of microbial infections in the human body such as UTIs, catheter-associated infections, or dental plaques [43]. *E. coli* can produce functional amyloids known as curli. These extracellular fibrils are involved in biofilm formation and may act as virulence factors as they interact with several of host proteins during infections. Curli fibrils are involved in bacterial attachment to surfaces, cell aggregation and are an important part of the extracellular matrix required for the formation of biofilms [44]. Curli fibrils are also considered important virulence factors as they interact with a wide range of host proteins, Curli are recognized by Toll-like receptors, leading to the activation of the innate immune system so it is considered pathogen-associated molecular patterns (PAMPs) [45]. CsgD is a transcriptional regulator as *Salmonella entericase* ovar *Typhimurium* that controls biofilm development [46]. The CsgD regulon includes genes involved in the production of curli fibers and the polysaccharide cellulose [47,48]. CsgD directly induces the curli subunit operon, while cellulose is activated via CsgD induction of the diguanylate cyclase gene adrA [49]. AdrA produces the second messenger cyclic-di-GMP, which activates the cellulose synthase and BcsA of biofilm formation [50,51].

B. cereus is an endospore forming bacterium that frequently found in dairy products and diary environments [52]. They have the ability to form biofilms and adhere to food processing equipment's [53].

B. cereus produces two types of toxins, emetic –responsible for emetic syndrome by bacteria during growth phase in food – and diarrheal causes diarrheal syndrome during bacterial growth in small intestine [54]. *B. cereus* secretes many virulence factors contributed to pathogenicity as collagenase, phospholipase, hemolysin, metalloprotease. Metalloprotease especially immune inhibitor A (Inh A) is Zn dependent enzymes that facilitate bacterial infilteration at the intestinal barrier and evasion of macrophages [55]. In industry, the best strategy to fight *B. cereus* biofilms is to prevent its formation either by reduction of the spore load in raw materials or by early detection and eradication of the newly developing biofilms [56].

Biofilm can be formed by one organism alone or mixture of two organism. Majority of microbes were existed as members of polymicrobial communities naturally [57]. Synergism between fungal or bacterial species lead to forming cooperative multi-species biofilms such as interactions of *Candida albicans* with *Streptococcus gordonii* in the oral cavity by directly binding of *C. albicans* protein Als3 to *Streptococcus gordonii* surface protein SspB [58], *C. albicans* with *S. aureus* in denture stomatitis infections. Also, *S. aureus* and *S. epidermidis* can form mixed biofilms in vitro and cause infected prosthetic joint [59].

V. Prevention of bacterial biofilm

Inhibition of bacterial biofilms occurs by several methods as follow:

1- Antibiotic Combination Treatments, cells inside biofilms have a much higher minimum inhibitory concentration (MIC) of antibiotics and provided through topical administration [60]. Combination antibiotic therapy such as sodium salicylate and N-acetylcysteine can used as anti-inflammatory, immune modulatory reagents, and used to break up the extracellular matrix and destroy biofilms but disadvantage was side effect of antibiotic [61,62].

2- Nanoparticles (NPs) are polymer- NPs, lipid- NPs and protein-based NPs that have used to overcome biofilms due to the unique mechanisms of the nano-systems, which are different from traditional antibiotics therapy [63]. Silver nanoparticles interact with bacterial membrane proteins, intracellular proteins, and phosphate residues in DNA, as well as to interfere with cell division, finally leading to bacterial death but the toxicity of silver nanoparticles is a serious problem that limits their use to certain sites [64].

3- Bdellovibrio and like organisms (BALOs) can inhibit biofilm formation. Gram-positive bacterial biofilms induce an intracellular transcriptome response in *B. bacteriovorus* and secrete of several proteases, hydrolases, and nucleases, which is associated with the degradative effect of BALOs and finally damage biofilms [65].

4- Modifying the surfaces of medical devices in order to eliminate biofilms such as metal materials because attachment of microorganisms to a surface is a first and critical step in biofilm formation. By using the materials resistant to microbial adhesion and incorporating antimicrobial agents (antiseptics, antibiotics, or metals) onto the surface, biofilm formation is impeded [66]. Vancomycin antibiotics are active against Gram-positive bacteria, might not be effective against the Gram-negative bacteria due to difference in cell

wall composition. Silver or silver–copper multilayer coatings used in various catheters and other medical devices, including urinary catheters, peritoneal catheters due to anti-infective efficacy.

5- Metal-containing therapeutic agents mostly used for treating tumors. ^{64}Cu-labeled coordination compounds are promising PET imaging agents for diagnosing malignant pathologies, including neck and head cancer, as well as the hallmark of Alzheimer's disease amyloid-β (Aβ) [67]. Copper containing coordination compounds are effective antitumor, antifungal, antimicrobial, antimalarial and anti-inflammatory agents because they are a less expensive. Copper is essential for formation and functioning of several enzymes and proteins, such as oxidase, cytochrome C and Cu/Zn superoxide dismutase, which are involved in the processes of respiration, energy metabolism, and DNA synthesis [68]. They are effective drugs which can replace classical platinum chemotherapy [69]. Also, sorbates can reduce bacterial biofilm formation due to cellular stress and increased toxin production. The effect of sorbate is increased by increasing acidity of the cell [70].

6- Protein denaturation and enzyme inactivation. Enzymes that degrade the biofilm extracellular matrix, such as dispersin B and deoxyribonuclease, may contribute to biofilm dispersal [71,72]. Enzymes that degrade the biofilm matrix may be useful as anti-biofilm agents such as fatty acid messenger, cis-2-decenoic acid, is capable of inducing dispersion and inhibiting growth of biofilm colonies. Fatty acid messenger,cis-2-decenoic acid, secreted by *Pseudomonas aeruginosa* induces cyclo-heteromorphic cells in several species of bacteria and the yeast *Candida albicans* [73].

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