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REVIEW

A review on anti-adhesion therapies of bacterial diseases

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Abstract

Background Infections caused by bacteria are a foremost cause of morbidity and mortality in the world. The common strategy of treating bacterial infections is by local or systemic administration of antimicrobial agents. Currently, the increasing antibiotic resistance is a serious and global problem. Since the most important agent for infection is bacteria attaching to host cells, hence, new techniques and attractive approaches that interfere with the ability of the bacteria to adhere to tissues of the host or detach them from the tissues at the early stages of infection are good therapeutic strategies.

Methods All available national and international databanks were searched using the search keywords. Here, we review various approaches to anti-adhesion therapy, including use of receptor and adhesion analogs, dietary constituents, sublethal concentrations of antibiotics, and adhesion-based vaccines.

Results Altogether, the findings suggest that interference with bacterial adhesion serves as a new means to fight infectious diseases.

Conclusion Anti-adhesion-based therapies can be effective in prevention and treatment of bacterial infections, but further work is needed to elucidate underlying mechanisms.

Keywords Adhesins · Antibiotic resistance · Infectious disease · Anti-adhesion therapy

Introduction

Bacterial infections are a major cause of mortality and morbidity worldwide. The excessive and incorrect use of antibiotics has led to the emergence of resistance, which is increasingly problematic for treatment due to increased antibiotic resistance. Thus, it has become increasingly important to develop new antimicrobials capable of withstanding the repertoire of bacterial resistance mechanisms. Adhesion of the pathogen to host cells or tissue is the first step during bacterial infection [1]. Alternatively, pathogens can colonize and invade host cells. Thus, anti-adhesion therapy is an important way to prevent or treat bacterial infections. Targeting bacterial virulence properties (e.g.. adhesion, colonization, invasion, production of toxins) is considered a valuable alternative strategy to antibiotic therapy [2], with the great advantage of combating the infectious process to reduce tissue damage [3]. Attachment of bacteria to the host cell surface can be inhibited by interfering with host receptor assembly, adhesion assembly or adhesion biosynthesis. Antibodies against bacterial adhesions can block surface epitopes required for binding [4, 5]. In this review, recent studies on anti-virulence therapy including the use of compounds that interfere with attachment or adhesion to the host tissue have been explord.

Overview of bacterial adhesion

Colonization is the most important step for pathogenicity in bacteria. It is necessary for the pathogen to stick to the host cell and tissue to start the infection. Colonization and subsequent internalization facilitate delivery of toxin and virulence factors to the host cell and helps the bacteria maintain their position and resist the host immunity. For example, many of Gram-negative bacteria employ different types of secretion system including type III, type IV or type VI to inject effector proteins into the host cells [1]. The clearance

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mechanisms vary given different regions of the human body. Urine flow in the urinary tract or airflow in the respiratory tract, action of mucociliary removal in the airway, and fallopian tube, the shedding of upper epithelial cell layers and the lining of tracts and tissue with antibodies, are natural cleansing mechanisms of the host, all of which inhibit the bacterial attachment. The hydrophobic molecule sphinganine, which is a host-derived anti-adhesion in innate immunity and a component of sphingolipids, decreases adhesion of *Streptococcus mitis* to buccal epithelial cells and *Staphylococcus aureus* to nasal mucosal cells [6]. These components act in such a way that they specifically bind to the pathogens entrapping them within the mucus blanket, and preventing attachment to the underlying epithelial cells [7]. The flow of mucus can reduce the pathogenic adhesion to the host cells [8]. In the gastric mucus, a sulfated component has been identified that can reduce bacterial binding to animal cells [9]. However, bacteria with their adhesives resist this mechanism. Furthermore, attachment of bacteria to the host makes it easier to get nutrients and delivery toxins and enzymes to the host cell [10]. Alternatively, weakening the tight association allows easier elimination of the pathogen by the immune system. Attachment of bacterial adhesives to an appropriate receptor in the host cell confers tissue tropism, allowing specificity of the interaction between the host and pathogen. This ensures that the bacteria take advantage of the environment most appropriate to their physiological and metabolic requirements and to utilization of the most desirable environment for growth and colonization, internalization or biofilm formation, depending on the bacterium [11]. There are multiple mechanisms for bacterial adherence to host cells and tissues. The first involves bacteria overcoming the electrostatic forces of the host cell. At physiological pH, both animal and prokaryotic cells have a negative charge, generating a repulsive force. The bacteria create a non-specific binding using hydrophobic molecules. Adhesion may also involve hydrophobic and other non-specific interactions, being mainly implicated in the initial 'reversible' phase of the process [12]. Bacteria may carry adhesions for more than one target surface and may employ more than one adhesion for binding to a substrate. Also, multiple adhesions can act in a concerted way and can be expressed at different stages during the infection [13]. Once in close contact to the mammalian cell, the bacteria can form stronger bonds with the surface. The adhesions involved in hard docking may be protein or polysaccharide-based [14]. Protein–protein interaction is a type of specific adherence, which involves protein adhesions and components of the extracellular matrix (ECM) or protein of the underlying structures which appear with wounds [15]. Other adhesions are neither protein nor sugar-based. *Streptococcus pneumoniae* contain phosphocholine in its cell surface which attaches to the receptor for platelet-activating factor. The binding of bacteria to the host often occurs in multiple adhesions, causing the appearance of tissue tropism in bacteria [16]. The most important adhesion, expressed by numerous bacteria, involves surface lectins, which they serve as virulence factors of the organisms. Blocking these lectins by their analogs or suitable carbohydrates for preventing and treating the microbial diseases is the aim of anti-adhesion therapy [4].

Interfering with surface receptor biogenesis

Several studies have suggested that physicochemical change of the bacterial surface can lead to impaired pathogen receptor biogenesis and decreased bacterial adhesion to host cells. *Yersinia, Pseudomonas, Klebsiella, Escherichia coli, Haemophilus*, and species of *Salmonella*, have chaperone–usher pili, which are recognized as the most important virulence factor. Inhibition of pilus assembly is a promising strategy for preventing infection [17]. Sec pathway is important for biogenesis of chaperone–usher pilus. This chaperone–usher system transfers subunits to the outer membrane. Designing a synthetic peptide mimicking the structure of pilus protein can inhibit or prevent pilus assembly (pilicides) by disrupting the chaperon–pilin complex [18]. Pilicides and curlicides are important factors that prevent synthesis and assembly of pili in the chaperone–usher pathway through different mechanisms and substitution of other metabolites [19].

Interfering with the host receptor biogenesis

Many bacterial adhesions and toxins use host glycosphingolipids receptors for binding to the membrane translocation [20]. Altering the structure of host cell glycosphingolipids has been proposed as an strategy to prevent or treat infections by utilizing inhibitors enzymes in the glycosphingolipids biosynthetic pathway [21]. In patients with lipid storage diseases, glycosylation inhibitors have been shown to be safe and effective [22].

Anti-adhesion therapy strategy

Antibiotics kill or stop the growth of susceptible bacteria, while nonresistant strains can continue to outspread and be transmitted to new hosts. Wild type strains compete with resistant strains in untreated individuals, acting to prevent extensive spread of the resistance [3]. Resistance to drugs arises spontaneously in a population through mutation. Persistent use of antibiotics will result in the death of all nonresistant bacteria. Therefore, only those with the mutation can propagate, resulting in the quick spread of resistance in

a population. In anti-adhesive therapy, sensitive bacteria are still viable, where resistance to antibiotic therapy has been observed to occur at a much slower rate [11]. By attaching to host cells, bacteria can resist the actions of cleaning mechanisms of the body, allowing the bacteria to reach a density whereby an infection can start. Anti-adhesion therapy would prevent this association, causing the pathogen to be removed by the host, thus preventing disease. Several strategies have been considered to destroy bacterial adhesion including coating the target substrate [23], modifying the surface anchoring [24], affecting adhesion biosynthesis [3], affecting glycosylation of the targeted substrate [25], use of anti-adhesion antibodies [26], or any type of adhesion analogs [27]. This novel therapeutics has aimed to prevent and treat bacterial infectious diseases.

Receptor analogs as anti-adhesion agent

Bacterial host interactions are frequently mediated by carbohydrates. Bacterial superficial carbohydrates contain glycoproteins, capsules and lipopolysaccharides, and host surface carbohydrates include glycoproteins and glycosphingolipids. Therefore, research has focused on the use of synthetic glycosides and glycomimetics that would act as anti-adhesives [28]. The presence of a large number of receptor analogs in the environment creates a competitive inhibitor state with the host receptors for interaction with bacterial adhesions. Hence, the true and actual interactions decrease between the bacterial adhesion and host receptors [4]. Mannose was first shown to be a receptor for enterobacteria. Similarly, special sugars can be of interest as receptor for special bacteria, contributing to the development of receptor-like carbohydrates, inhibiting the adhesion of pathogens to host cells and tissues. Studies suggest that, in vivo, the concentrations of sugar analogs for inhibition of adhesion are usually high due to their relatively low affinity for the target adhesion. This problem has been solved by linking the saccharide to hydrophobic residues. Affinity can be increased by attaching much of the saccharide to an appropriate carrier. For example, the affinity of alkyl-substituted mannose residues is 100 times higher than that of mannose for adhesion of FimH of *E. coli* [29]. FimH, the adhesive subunit at the tip of type 1 pili, is crucial for colonization and invasion to bladder tissue and is a key virulence factor in UTIs. Pharmacokinetic studies have revealed that these methods are appropriate for UTI treatment in a preclinical murine model, with reductions in colony-forming units comparable to the those obtained by antibiotic ciprofloxacin [30]. Crystallographic studies and NMR relaxation analysis have indicated that the lectin domain of the adhesion contains a relatively deep sugar-binding pocket lined by aromatic lipophilic residues at the rim (the tyrosine gate, formed by Tyr48, Tyr137, and Ile52) along with established butyl α-D-mannoside 1 as a strong antagonist [31]. The first study of anti-adhesive effect of mannoside-based host receptor analogs began in 1970s in a murine model of UTI. Because of weak inhibition of this anti-adhesive, two strategies were used to improve the efficacy of FimH inhibitors: logical design of monovalent inhibitors with agglutinating components and synthesis of multivalent compounds with increased binding avidity to enhance affinity [32]. Administration of methyl K-mannoside together with *E. coli* expressing the mannose-specific type 1 fimbrial lectin into the bladders of mice reduced the extent of bladder colonization by Uropathogenic *E. coli* (UPEC) [3]. Two combinations including α-methyl-galactoside and α-methyl-fucoside are inhibitors of lectin (LecA and LecB). Further, *Pseudomonas aeruginosa* adhesions reduced the damage and mortality in a murine model of bacterial-induced lung damage. This was most likely due to reduction of *P. aeruginosa* adhesion, reducing bacterial burden and dissemination [33]. Sialyl-3P-lactose [NeuAc K(2–3)GalL(1–4)Glc] is a specific safe and selective anti-adhesive agent for adhesion of *Helicobacter pylori* to human gastric tissue culture cells [34]. However, this method has not been entirely successful in clinical trials. The reason for this is that multiple adhesions are utilized by a pathogen during an infection. These have diverse specificities, and therefore, require multiple inhibitors to prevent adhesion. The drug combination of multiple sugar receptor analogs is expected to be the only practical strategy for this type of therapy in the future. Another problem arises here, however. The cells of various tissues of the body, such as gastrointestinal epithelial cells, constantly turn over and experience a high flow rate, which may dislodge the sugar mimics, removing the protection. Other defensive mechanisms against bacterial infection include physical barrier against colonization by pathogens. Mucus contains a variety of mucin glycoproteins secreted by the intestinal epithelium. Mucins act by binding and immobilizing bacteria [35].

Peptide-based inhibitors

Streptococcus mutans expresses a surface protein streptococcal antigen (SA) I/II. It is the key attachment factor for *S. mutans* which binds to salivary receptors adsorbed on the hydroxyapatite matrix of the tooth surface, where monoclonal antibodies raised against (SA) I//II can prevent tooth colonization [36]. For this area, peptide has been designed, in response to which the inhibition of the connection declines by 65–85%. This approach is useful in preventing caries as well as other streptococcal infections [37]. MAM7 is another promising candidate for developing a peptide-based anti-adhesive. MAM7-coupled polymer beads have been used to decrease the surface attachment and infection of pathogens including *Yersinia pseudotuberculosis*, Enteropathogenic *E. coli* (EPEC), *Vibrio cholerae*,

and *Vibrio parahaemolyticus* [38]. Fuzeon is a peptide-based HIV fusion inhibitor that blocks the binding and fusion of viral particles to host cells [39]. Factors need to be considered in the design of peptide-based anti-adhesion, including the stability in the host environment and their binding avidity [40]. Importantly, some adhesions may trigger signaling pathways by binding to host receptors. This may cause unwanted side effects, and therefore, should be considered in preclinical studies on peptide-based inhibitors [41].

Adhesion analogs as anti-adhesion agents

Adhesion analogs also inhibit attachment of adhesins to host cells, but there is an increased chance of toxic and immunogenic side effects to healthy individuals. Furthermore, large quantities of these molecules would need to be employed to significantly reduce bacterial adhesion. An anti-adhesion peptide produced against *S. mutans* superficial proteins, when applied to the teeth of human volunteers, prevents colonization by *S. mutans* [42]. Studies suggest that this method may be widely successful for anti-adherence therapeutics when applied to specific pathogens.

Dietary inhibitors of adhesion

Many food components have been isolated and demonstrated to have a protective effect against bacterial infection in vitro [1]. For example, cranberry juice protects against bacterial infections, in particular UTIs. Proanthocyanidins and polyphenols have proved to be the bioactive compounds contained in cranberries [43]. Proanthocyanidins inhibit the adhesion and co-aggregation of *Porphyromonas gingivalis, H. pylori* and, UPEC [44]. Polyphenols and proanthocyanidins can bind to flagella and pili, thus inhibiting bacterial surface attachment, aggregation into biofilms and swarming motility. Other food ingredients such as coffee, tea, wine, and plantains contain compounds with anti-adhesion properties [2]. Food-stuff containing either a mixture of inhibitors or an inhibitor with a broad spectrum of activity could be especially selective. These dietary items are good candidates for anti-adhesion studies. Nevertheless, caution should be exercised in consuming these foods because these compounds may have bactericidal or bacteriostatic effects and selective pressures imposed by such compounds are undesirable and should be avoided [45].

Anti-adhesion antibodies and vaccines (adhesion-based vaccines)

Many studies have indicated use of antibodies against bacterial adhesions, which is used as an anti-adhesion strategy. The host can be directly or passively immunized through bacterial adhesion. Immunization can be done by a DNA vaccine encoding the adhesion [1]. DNA vaccines contain DNA that encodes the antigen of the target protein, which upon their expression in the host, are able to create protective immunity. Vaccines induce humoral and cell-mediated immunity against a pathogen. Prevention of bacterial infections based on adhesion-based vaccinations can be achieved through multiple mechanisms. Many bacteria express surface proteins and pili and other adhesive factors, hence adhesion should be disrupted by inducing an antibody response toward the attaching agent [45]. The problem is the high degree of variation in the protein sequence among strains, due to their allelic variations [46]. Because of the emergence of multidrug-resistant strains, treatment of some pathogens like *Salmonella enterica* serovar Typhi is complicated. The *S.* Typhi adhesion T2544 is an important factor in the interaction between bacteria and the host. T2544 is highly immunogenic, and dramatically increases the level of IgG and secretory IgA in immunized mice. For this reason, it is potentially a good candidate for vaccine development [47]. Definitely, apart from T2544 factor, there are other adhesion factors including the type IV pili, so the treatment of the disease has not been completely successful [48]. In a study, Immunization with FimH-based vaccines against UPEC prevented 99% of infections in a murine cystitis model. Immunization with FimH adhesion–chaperone complex in combination with an adjuvant elicited a strong IgG antibody response in monkeys and protected the animals against UPEC infection [49]. *Bordetella pertussis* contains filamentous hemagglutinin and pertactin adhesions on its surface, where both epitopes are used in vaccines effective against whooping cough [50]. Antibodies generated against these adhesions inhibit adherence of the bacteria to the cells of the respiratory tract [51]. In *S. pneumoniae*, by reducing colonization, an intranasal vaccine of pneumococcal surface adhesion A, has successfully reduced nasopharyngeal carriage rates in mice [52]. Outer membrane proteins of *Salmonella enterica* serovar Typhi [47], the clumping factor A and fibronectin-binding protein A in *S. aureus* [53], are other bacterial adhesion proteins with potential as vaccine targets. Conjugate polysaccharide vaccines like pneumococcal vaccination result in reduced nasopharyngeal colonization by *S. pneumoniae* strains [54]. Meningococcal polysaccharide vaccination reduces carriage of *N. meningitidis* [55]. In these cases, transudation of immunoglobulin into the nasopharynx causes reduction in bacterial carriage. In addition to capsular polysaccharide vaccine, reduction has also been induced by an outer membrane vesicle vaccine. *Neisseria lactamica* outer membrane vesicle vaccine triggered reduced colonization of *N. lactamica* [56]. For embedding into host membranes, some bacteria secrete their own receptor into the host cell, like translocation of the intimin receptor in Enterohemorrhagic *E. coli* (EHEC) for attachment onto

epithelial cells. This process can be blocked using antibodies generated through vaccination [57]. Enterotoxins of Enterotoxigenic *E. coli* (ETEC) are a major cause of diarrheal disease in humans and other animals. Studies suggest that rabbits immunized by an epitope from the A subunit of shiga toxin (STa) and B subunit of heat-labile (LT) toxin and FaeG, the major subunit of *E. coli* K88ac fimbriae, generated anti-STa antibodies, anti-LT and anti-K88ac, thus inhibiting adhesion of fimbrial *E. coli* to small intestinal enterocytes [58]. *P. aeruginosa* is an opportunistic pathogen which is becoming increasingly resistant to traditional antimicrobials. Cachia and Hodges described a synthetic peptide anti-adhesion vaccine against small peptide structural element found in *P. aeruginosa* strain K (PAK), which binds to the host epithelial cells. This process causes elevated anti-adhesion antibodies against multiple strains [59]. The proper vaccine should be able to stimulate both cellular and humoral immune responses. This goal can be achieved by having adhesion antigens communicate with outer membrane vesicles. This strategy has been used to prepare a vaccine against *Neisseria meningitidis*. DNA vaccines have also been generated against *S. aureus* [60]. *S. aureus* binds to host cells by a number of surface proteins. For example, the collagen-binding protein (CNA), the major adhesin of *S. aureus*, was used to immunize Balb/c mice. The injection of this protein has stimulated both antibody and cell-mediated immune response in the mouse. A multiprotein DNA vaccine against *S. aureus*, consisting of a series of plasmids expressing the enzyme sortase (Srt), fibronectin-binding protein A (FnBPA), and clumping factor A (ClfA) has triggered both antibody production and T-cell response against *S. aureus* [61]. The most major incompetency of this method is the presence of a variety of adhesion in bacteria, making its treatment difficult. The use of anti-adhesion antibodies or vaccines may still be effective. Antibodies can be involved in opsonization, so they can play a significant role in triggering the complement mediated bacteriolysis. However, antigenic variability of bacterial adhesions can potentially impair the efficacy of anti-adhesion antibodies [62].

Inhibitors of adhesions & receptors

To prevent colonization and infection of bacteria, we need to block adhesion of bacteria and inhibit the attachment to host cells. There are many potential targets for drugs that can disrupt the formation of these molecules. Pilicides are indeed toxins inhibiting the chaperone–usher pathway in Gram-negative microorganisms. For instance, the inhibitor targets pilus chaperone PapD, thereby reducing the adhesion to cell lines by 90% [63]. These pilicides inhibit curli formation in UPEC by preventing the polymerization of protein CsgA and FimC, the chaperone protein of the type I pili [64]. Sortase in Gram-positive bacteria catalyzes the formation of surface adhesions and pili, Thus, sortase is the target for several drug inhibitors [65].

Sublethal concentrations of antibiotics

Studies suggest that concentrations of antibiotics less than the amount to kill the bacteria affect the biochemistry of adhesions and the properties of the bacterial surface and subminimal inhibitory concentration (sub-MIC) of antibiotics can reduce adhesion to numerous surfaces [66]. Sub-MIC levels of ciprofloxacin caused a reduction in the hydrophobic nature of the bacterial surface in UPEC strains [67]. Sub-MIC of β-lactams piperacillin and imipenem have also had an inhibitory effect on adherence of *P. aeruginosa* [68]. Sub-MIC concentrations of antibiotics have reduced damage to the mucosal surface by *Haemophilus influenzae* [69]. (Sub-MIC) antibiotics may actually increase the levels of adhesion of certain bacteria, such as the attachment of UPEC to catheters [70]. Sub-MIC oxacillin for treatment of *S. aureus* has shown significantly increased adherence [70]. Conversely, the effect of sub-MIC diminished adherence. Rifampin treatment has decreased fibronectin binding of *S. aureus* and reduced attachment of bacteria to the surface [71]. Another problem with the use of sub-MIC antibiotics is the emergence of bacterial resistance, where under sub-MIC conditions, resistance is more likely to occur [72].

Dietary supplements as adhesion inhibitors

Some dietary supplements inhibiting bacterial adherence can be found in natural foodstuff. These inhibitor dietary supplements can be extracted and used as anti-adhesion agents. The mechanism of action is unknown, but they may be receptor analogs and adhesion inhibitors [2]. Cranberry is the most studied dietary supplement, particularly in terms of UTIs and dental decay. It has been shown that the cranberry polyphenols are capable of reducing the attachment of a range of bacteria, including *E. coli* [73], *N. meningitidis* [74] and *S. mutans* [75]. According to a study, Women who consumed cranberry juice over extended periods, have displayed reduced incidences of bacteriuria [76]. Furthermore, milk contains oligosaccharides, antibodies and glycoproteins that can reduce bacterial adherence. Many bacteria are known to bind to such compounds, whereby their ability to adhere to and colonize the host tissue is inhibited. Breast-feeding of human infants has reduced rates of diarrhea via inhibition of bacterial adherence in infant [77]. Human milk is rich in oligosaccharides as well as related compounds, which inhibit the binding of both the common enteric pathogens (*E. coli*) and pathogenic species (*V. cholerae* and *Salmonella fyris*) to

epithelial cell lines [78, 79]. Bovine Muc1 derived from cow milk efficiently prevents bacterial infection. It is not effective in inhibiting attachment of Gram-positive organisms such as *Bacillus subtilis* and *S. aureus*, but it inhibits the attachment of Gram-negative pathogens (*E. coli* and *Salmonella* Typhimurium) [80].

Probiotics as anti-adhesive agents

A convenient and inexpensive procedure to achieve the necessary polyvalency of inhibitive epitopes is their heterologous expression on the surface of probiotic bacteria. Probiotics are useful bacteria that prevent pathogens from reaching a critical density required to cause disease. They can act to reduce the binding of pathogen bacteria. Probiotic bacterial strains can displace pathogenic bacterial antigen and they compete with the pathogen for vital nutrients for growth [81]. Probiotics have been specifically designed to mimic sugars on host receptors, thereby blocking the host cell binding of toxins released by pathogenic bacteria including *V. cholera,* ETEC and shiga toxin-producing *E. coli* (STEC) [82]. Consumption of probiotics like certain strains of bifidobacteria can protect against an otherwise lethal infection of *S.* Typhimurium [83]. It is, however, difficult to understand the mechanism of action of probiotics. Probiotics may inhibit pathogen adherence through influencing other components of pathogenesis, such as the production of antimicrobial substances like lactic acid and bacteriocins [84] and activation of the innate immune system [85].

Glycoconjugates and glycomimetics as microbial anti-adhesives

The most important factor for pathogenicity of microorganisms is the binding to the host cell with the adhesion factors. Bacterial adhesions, located on the bacterial surface or on pili and fimbriae, interact with specific glycans on the host tissues. Inhibition of this attachment is a target for anti-adhesion therapy in several infective diseases. Use of suitable compounds that are resistant to environmental conditions is very important. For example, natural compounds can limit resistance to enzymatic degradation. Therefore, appropriate compounds should be used to solve this problem. The use of carbohydrate mimics (glycomimetics) as a replacement for natural sugars potentially allows higher metabolic stability and also higher selectivity towards the desired protein target [4]. Effective anti-adhesion therapy requires high-affinity monovalent lectin multivalent structures incorporating several copies of ligands of moderate affinity on a polyvalent scaffold (dendrimer, polymer, nanoparticle) [86] (Table 1).

New approachwa in anti-adhesion therapy

Organosilane nanoparticles

One of the anti-adhesion strategies to reduce the binding of bacteria to the host cell is modification of surfaces by nanoparticulate coating. In 2017, a study was conducted in Greece, where the biofilm biological cycle of a number of pathogens including *S. aureus, S.* Typhimurium, *E. coli* O157:H7, *Listeria monocytogenes*, and *Yersinia enterocolitica* was monitored on stainless steel and glass surfaces, with or without nanocoating. Organosilane nanoparticles affected the bacterial attachment, and the subsequent biofilm formation reduced the bacterial attachment [108].

Nanostructured mesoporous carbon polyethersulfone composite ultrafiltration membrane

In 2016, Yasin Orooji and colleagues studied the novel polyethersulfone (PES) ultrafiltration membrane containing of mesoporous carbon nanoparticles (MCNs), which exhibited the highest protein adsorption resistance and bacterial attachment inhibition property. Surface modification by incorporating antibacterial agents into the polymer membrane matrix is an effective approach to inhibiting the growth of microorganisms [109].

Live-cell nanoscopy in anti-adhesion therapy

Antibodies and synthetic peptides can target host surface proteins to inhibit the different stages of biofilm formation, from initial attachment to biofilm accumulation [110]. Nanoscopy techniques have offered unprecedented opportunities to study the location and motion of single molecules in cells. Atomic force microscopy (AFM), also called force nanoscopy, is capable of capturing and measuring the cell surface and measuring the interaction forces between single cells and single molecules required for biofilm formation [111]. In this technique, living microbial cell is attached to the AFM probe, as a result, scientists can examine interactions between the cell and target surface and evaluate the influence of inhibitors on these interactions. AFM-based nanoscopy has been used to gain insight into the mechanism by which cranberry juice inhibits the adhesion of clinical UPEC [112]. The *S. aureus* collagen-binding protein (Cna), is involved in adherence to collagen. Further, Herman-Bausier et al. [113] demonstrated the anti-adhesion activity of monoclonal antibodies (mAbs) against Cna by nanoscopy techniques. Some mAbs were also able to block Cna binding to the complement

Table 1 Examples of anti-adhesion studies as inhibitors bacterial pathogens

Material group or anti-adhesion	Anti-adhesive mechanism	Year	Location	Authors	Animal	References
Multivalent adhesion molecule (MAM7) coupled to polystyrene microbeads	Blocking pilus assembly or function in *P. aeruginosa*	2017	Birmingham	Roberts et al.	In vivo rat model	[87]
PilQ/PilA antigen of *P. aeruginosa* (vaccine)	Anti-pili in *P. aeruginosa*	2017	Iran	Gholami et al.	In vivo mouse model	[88]
Chitosans	Inhibition of the growth and adhesion of human uropathogens	2017	Italy	Campana et al.	In vitro	[89]
Salvianolic acid B	Anti-pili of *N. meningitidis*	2016	Finland	Huttunen	In vitro	[90]
Quercetin-mediated nanoparticles	Anti-adhesive activity against *B. subtilis* biofilm	2016	Egypt	Raie et al.	In vitro	[91]
Phaleria macrocarpa	Anti-adhesion and anti-biofilm agent against *S. mutans*	2015	Malaysia	Heana et al.	In vitro	[92]
Essential oils (EOs)	Anti-adhesive potential against a foodborne pathogen *Salmonella* strain	2015	Tunisia	Miladi et al.	In vitro	[93]
Monoclonal antibody	Against pneumococcal type I pilus (RrgA)	2015	Italy	Amerighi et al.	In vitro	[94]
Designed peptides	Blocking the binding of AAF-II EAEC	2015	India	Gupta et al.	In vitro	[95]
Calixarene-based glycoclusters	Anti-adhesive *of P. aeruginosa*	2014	France	Boukerb et al.	In vivo mouse model	[96]
Cranberry bioactives	P-fimbrial of *E. coli*	2013	Not determined	Kaspar et al.	Ex vivo	[97]
Synthetic-mannosides	FimH of *E.coli*	2013	Germany	Fessele et al.	In vitro	[98]
Flavonoid rich extract of *Glycyrrhiza glabra* (GutGard)	*H. pylori* (inhibit DNA gyrase, dihydrofolate reductase, protein synthesis)	2012	India	Asha et al.	In vitro	[99]
S-carboxymethylcysteine (*S*-CMC)	Reducing the expression of host receptors for *S. pneumoniae*	2011	Japan	Sumitomo et al.	In vitro	[100]
High molecular weight coffee components	Inhibiting the ability of *S. mutans*	2010	Italy	Stauder et al.	In vitro	[101]
Cranberry	P-fimbriae of *E. coli*	2010	France	Howell et al.	ex-vivo/in vivo	[102]
Lactobacillus rhamnosus GG	Reduction of adhesion and cytotoxicity of *S. Typhimurium*	2009	USA	Burkholder et al.	In vitro	[103]
Wine components	Anti-adhesion and anti-biofilm activity against *S. mutans*	2009	Italy	Daglia et al.	In vitro/ex vivo	[104]
Sialyloligosaccharides (SOS)	Inhibition of *V. cholerae* toxin (Ctx) binding to GM1-OS	2009	United Kingdom	Sinclair et al.	In vitro	[105]
Monosaccharide	Inhibition of adherence by *P. aeruginosa* to canine corneocytes	2008	England	McEwan et al.	In vivo	[106]
Ceramic-composite	*S. mutans*	2007	Germany	Rosentritt et al.	In vitro	[107]

system protein C1q and the extracellular matrix protein laminin [114]. Researchers have designed peptides that can prevent biofilm formation of *S. aureus*. The surface adhesion SdrC mediates biofilm accumulation by weak homophilic bonds. They discovered that β-neurexin which is peptide derived from the neuronal cell can inhibit SdrC attachment to surfaces and biofilm formation. Live-cell nanoscopy has significantly contributed to assessing the inhibition of bacterial adhesion.

Characterization of non-dialyzable constituents from cranberry juice

Non-dialyzable material (NDM) of cranberry extract has anti-adhesion properties against bacteria such as UPEC *H. pylori* [115], and *Staphylococcus epidermidis*. According to a study, the biofilm formed on soft contact lenses microbial keratitis is caused by Gram-positive bacteria in 27%, Gram-negative bacteria in 11%, and multiple microbes in 13.8% of

cases [116]. Non-dialyzable material (NDM) reduces formation of biofilm on soft contact lenses.

Advantages and disadvantages of anti-adhesion therapy

The essential step in infection is microbial adhesion mediated primarily by protein–carbohydrate interactions. Prevention of such interactions has become a promising target for anti-adhesion therapy in several infective diseases. Most successful anti-adhesive materials consist of polyvalent glycoconjugates, while monovalent protein–sugar interactions are often weak [117]. Anti-adhesion therapy does not increase antibiotic resistance, since it only inhibits bacterial binding to surface without affecting microbial viability. This approach prevents colonization and biofilm formation, but does not kill the invading pathogen, and therefore, selective pressure as well as resistance to anti-adhesin do not develop [4]. It is clear that the presence of multiple bacterial adhesions and the lack of appropriate methods to deliver the inhibitors for all adhesions are a major hindrance to anti-adhesion therapy. Other problems are low affinity of free receptors to the bacterial ligands, and presence the adhesins of common epitopes with human proteins. Nevertheless, it is possible that mutations could occur and affect the efficacy of anti-adhesion compounds. These would also directly affect the pathogen's ability to bind to the host receptor. Clearly, point mutations in bacterial adhesions can influence tissue tropism in human body. Consideration of this issue informs us in designing strain-specific and species-specific anti-adhesive compounds, thus avoiding side effects caused by changes in the microbiota. Another benefit of this technique is resistance to environmental conditions. Furthermore, anti-adhesion compounds are not bactericidal, and they do not have harmful effects on the host such as the release of bacterial toxins and endotoxins.

Concluding remarks

Misuse of antibiotics has led to the development of resistant strains, and the infection that has already been curable has now become a problem. Therefore, alternative therapies are really needed. Anti-adhesion therapy involves attempts for blocking adherence, quorum sensing, biofilm formation and virulence. These have benefits over traditional antibiotics by virtue of inhibiting pathogenicity without killing bacteria. This, in turn, hampers the development of subsequent increased resistance in a bacterial population by removing the selective pressure for such mutations, giving key advantages over classical drugs. Bacteria utilize a variety of adhesions during the process of adherence, hence, multiple molecular interactions may need to be inhibited to maximize the removal of the pathogen from the body. As a result, despite the potential advantages of anti-adhesion therapy, there have been failures in some cases. This may account for the lack of extensive use of such treatment, despite initial successes. On the other hand, tissues are composed of multiple cell types with varying receptors for bacterial adhesions. For developing the use of anti-adhesin therapy, it may be better to focus on simple tissues such as the bladder and nasopharynx, rather than more complex tissues of intestinal tract, where the associations between bacteria and the host are more intricate. Better knowledge of the stereochemistry of these adhesions and their receptor–ligand interactions will allow better design of anti-adhesive agents. Broad specificity inhibitors that block multiple targets, such as those found in dietary products or a combination of several distinct agents that target separate adhesions seem to be a decent solution. These will require significant testing until they become fully licensed for use in healthcare. They must also prove to be as effective as present antibiotics.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

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