Anti-adhesion therapy, a promising alternative in the infections treatment.

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ABSTRACT

Objective: Antibiotic resistance (AR) represents one of the most important health problems worldwide due to the fact that it significantly lowers the number of effective antibacterial agents. Many mechanisms were studied to reduce emerge of AR, one of these is the use of Anti-adhesion

Methods: keywords were used to search Most of the subject available articles. Following that, a grammatical examination was done for the vocabulary associated with the literature review.

Results: Anti-adhesion agents represent vital approach to stop or treat bacterial infections. As these agents focus on bacterial virulence and pathogenicity properties (e.g. adhesion and colonization). These agents considered a perfect alternative for an antibiotic, with the infectious process inhibiting advantage in the first step to reduce the damage. These agents inhibit bacteria attachment to the surface of the host cell through interfering with the assembly of host receptor, bacteria-host cell assembly or adhesion biosynthesis. Bacterial adhesions antibodies can prevent surface epitopes required for bacteria-host cell attachment by the application of anti-adhesion strategy to decrease AR or reduce the need for the effective antibiotic doses.

Conclusions: Anti-adhesion therapy includes efforts for preventing adherence, reduces virulence, and biofilm formation. These have advantages over classical antibiotics through blocking pathogenicity without destroying bacteria and it also have a synergistic effect when applied with antibiotics

Keywords: Anti-adhesion therapy, Adhesions, Antibiotic resistance, Anti-adheres mechanisms.
1. Introduction
Antibiotic resistance developed when microorganisms such as bacteria, fungi or viruses not affected when they exposed to antibiotic drugs that used as standard practice to treat the infections they cause. These microorganisms cause persist of infections in the body and elevate the risk of spreading to other people. In both developing and developed countries, bacterial infections considered one of the major cause of morbidity and mortality. The irrational excessive use of antibiotics results in antibiotic resistance, which substantially reduces the number of effective antibacterial agents. Thus, the need increased to search for modern antibiotics that have the ability to bypass the mechanisms of microbial resistance. The bacterial-host cells or tissue adhesion represent the initial step of the infection\(^1\).

Anti-adhesion agents represent a significant strategy to block or treat bacterial infections. As these agents focus on bacterial virulence and pathogenicity properties (e.g. adhesion and colonization). Such agents considered a good substitute for antibiotics\(^2\), with the benefit of infectious process inhibiting to reducing the damage\(^3\). These agents inhibits the bacteria-host cell attachment through interfering with receptor assembly, receptor adhesion assembly or receptor adhesion biosynthesis of the host. These agents inhibit bacterial attachment to the host cell surface by interfering with the assembly, adhesion assembly or biosynthesis of the host receptor. Bacterial adhesion antibodies may prevent the brequired surface epitopes for attachment\(^4\).

2. Overview of bacterial adhesion
Adhesion and colonization are important steps for bacteria pathogenicity. Adhesion is important process for the pathogen to initiate the infection. Colonization and subsequent steps promote virulence and toxin delivery to the cells of the host and also support the bacteria in place and resist the host immunity. Several species of gram-negative bacteria for example inject various types of proteins into the host cells to maintain its position\(^1\). Human body have different clearance mechanisms that inhibit bacterial adhesion, for example flow of urine in the urinary system or respiratory tract airflow and upper epithelial cell shedding of fallopian tube are all natural cleansing mechanisms of the host. The sphinganines, which are hydrophobic sphingolipids molecule act as anti-adhesion ability especially in innate immunity and play a major role in decreases adhesion of Streptococcus mitis and Staphylococcus aureus to the mucosal nasal cavity and buccal epithelial cells respectively\(^5\). Sphinganines attaches to the infectious agents specifically, seize them in the mucus as a result prohibiting there attachment to the sub epithelial cells\(^6\). The host cells also inhibit the pathogenic adhesion by mucus flow and removal mechanisms\(^7\). Certain sulfated component has been identified in the gastric mucus have ability to inhibit the bacterial cell attachment to the host cell\(^8\). However, bacteria possess anti-adhesives resist this mechanisms as bacteria need the host for nutrients and replication\(^9\). Bacterial adhesives attachment with an appropriate receptor in facilitate the interaction between the pathogen and host. Thus bacteria will recruit the host environment to support their physiological and metabolic requirements facilitate pathogen growth, colonization, internalization and biofilm formation\(^10\).

Bacteria binding to the cell take place in multiple adhesions. Bacterial adherence mechanisms include:
1. The bacteria bypass the electrostatic repulsion forces as both host and bacteria cells are negatively charged at physiological pH producing a repulsive
force thereby creating a non-specific attachment by utilizing hydrophobic molecules. Attachment includes hydrophobic as well as other interactions that are non-specific which are primarily involved in the initial 'reversible' phase of the cycle\(^{(11)}\). Bacteria can be adhered to further than one target surface and can use more than one adherence to attach to a substrate. Multiple adhesions can be expressed at various levels through the infection\(^{(12)}\).

2. Hard docking adhesions can be polysaccharide or protein\(^{(13)}\). Interaction of protein to protein is one of a specific adherence that demand protein adhesions to the structural extracellular matrix or proteins that emerging with the wounds\(^{(14)}\).

3. Phosphocholine connections are other adhesions, since Streptococcus pneumonia includes phosphocholine on their cell surface which in turn bound to the receptor of the platelet-activating factor\(^{(15)}\).

4. The most important adhesion mechanism involve surface lectins, which act as virulence factors for infectious agents and prevent such lectins through their analogs or appropriate carbohydrates to prevent and treat the infections is the goal of such strategy\(^{(4)}\).

3. Anti-adheres mechanisms

3.1. Interfering with biogenesis of the surface receptor

The changing in the surface physical and chemical properties of the bacteria will degrade receptor biogenesis of the pathogen and reduce bacterial-host cells adherence. Chaperone-usher-pili, considers one of the most important virulence factor present in *Klebsiella, Escherichia coli, Yersinia, Pseudomonas, Haemophilus,* and *Salmonella* species. Pilus assembly inhibition considered a creative strategy for infection prevention\(^{(16)}\).

An artificial peptide Designing similar to pilus protein structure can prevent or inhibit the assembly of the pilus through disrupting the caperon-pilin complex\(^{(17)}\). Curlicides and pilicides considered an important factors interferes with the pili synthesis and assembly in the chaperone-usher by many pathways and various metabolic compounds\(^{(18)}\).

3.2. Interfering with the biogenesis of the host receptor

Most adhesion molecules and toxins of the bacteria use host glycosphingolipid receptors to bind to the membrane\(^{(19)}\). Host cell structural alteration of glycosphingolipids has been proposed as one of the strategies to treat or even prevent infections through utilization of inhibitory enzymes in the biosynthetic pathway of the glycosphingolipids\(^{(20)}\). In lipid storage disorders patients, enzymatic and non-enzymatic glycosylation inhibitors have been shown to be effective and safe for infection prevention\(^{(21)}\).

4. Strategy for anti-adhesion therapy

Sensitive bacteria growth is prevented by antibiotics, while resistant strains may keep increasing and even transmit to new hosts. In untreated individuals, normal (wild type) strains clash with resistant strains and work to avoid resistance widespread\(^{(3)}\). Antibiotics resistance spontaneously arises in a populations by random mutation. Constant antibiotic use will lead to the destruction of all sensitive microbes. Only the organisms with the proper mutation can survive. There for, quick spreading of resistance in a population will be the final result. As for anti-adhesive therapy, viability of the sensitive bacteria will be observed, and antibiotic treatment resistance reported to happens at a quite slower rate\(^{(10)}\). Through host cells attaching, bacteria can withstand the body's behavior.
of cleaning processes, causing themselves to achieve a density in which infection can occur. As for anti-adhesion therapy, it would eliminates this interaction, which allows the host to expel the pathogen and thus prevents disease. A variety of strategies have been proposed to kill bacterial adhesion, such as the covering of the target substrate\(^\text{22}\), affecting adhesion biosynthesis\(^\text{3}\), modifying the surface anchoring \(^\text{23}\), affecting the targeted substrate glycosylation\(^\text{24}\), use of adhesion analogs or anti-adhesion antibodies\(^\text{25,26}\).

All of these novel strategies aimed at preventing and treating infectious diseases of the bacteria.

4.1. Receptor analogs an anti-adhesive agent

Interactions of bacterial to the host mostly mediated via carbohydrates. Superficial carbohydrates of the bacteria involve glycoproteins, lipopolysaccharides and capsules, whereas carbohydrates of the host surface contains glycosphingolipids and glycoproteins. Research has therefore concentrated on synthetic and glycomimetics glycosides use serve as anti-adhesives\(^\text{27}\). Availability of a significant amount of receptor analogs throughout the microbial environment generates a competitive inhibitor state for host receptors that interacts with adhesion of bacteria\(^\text{4}\). Mannose has shown to be an enterobacteria receptor. Many unique sugars may be used as receptors for special bacteria and it may contribute to receptor-like carbohydrates development. Inhibit the adherence of infectious agents to host cells.

Several studies revealed that sugar analogs concentrations for adhesion inhibiting are generally high due to the fairly low affinity of these molecules to target adhesion. Such a problem can be solved through attaching saccharide and hydrophobic residues together. Affinity may be enhanced through connecting the saccharide to the correct carrier. The mannose affinity is 100 times higher for adhesion of \textit{E. coli}'s FimH when attached to Alkyl group to become Alkyl-substituted mannose\(^\text{26}\). Pharmacokinetic tests have shown that such approaches are effective for UTI therapy in the murine model, with colony-formation decreases compared to those achieved through the ciprofloxacin\(^\text{27}\).

Two approaches have been used to increase the effectiveness of FimH inhibitors due to the anti-adhesive weak inhibition (monovalent inhibitors logical design with agglutination components and multivalent compound formulation with enhanced attachment avidity to improve affinity)\(^\text{28}\). Methyl K-mannoside Administration altogether with \textit{E. coli} expressing mannose-specific type 1 fimbrial lectin in the mice bladder reduced its UPEC colonization\(^\text{3}\). Furthermore, anti-adhesions decrease the mortality and damage in the lung damage murine model induced by \textit{P. aeruginosa} bacteria. This was appropriate due to the adhesion reduction of \textit{P. aeruginosa}, which result in bacterial burden and spread reduction\(^\text{29}\). Researches demonstrated that Sialyl-3P-lactose is a is a pretty specific, selective and, safe molecule against \textit{Helicobacter pylori} adhesion to human gastric cell culture\(^\text{30}\).

Despite that, this was not completely successful in trials. The possible explanation might be that numerous adhesions were consumed by the microbes through infection. Different specificities has been added to this and therefore preventing adhesion takes several inhibitors. A drug These have different specificities and therefore preventing adhesion takes several inhibitors. A mix of several sugar receptor analogs is considered to be the very first realistic approach for such a type of treatment in the future, which is yet to be resolved.

Cells of different tissues, including gastrointestinal epithelial, are constantly experiencing a high flow rate, that can removes sugar through mimicking protection
removal. Another protective mechanism versus bacterial diseases is the physical barrier versus pathogen colonization. Various mucin glycoproteins are found in mucus that are secreted from the intestinal epithelial cells. Mucins, in turn, act through attaching and disable bacteria and therefore functions as an adhesion inhibitor\(^{31}\).

### 4.2. Peptide inhibitors

Streptococcus mutans express the protein antigen (SA) I/II, which considers an important factor for S.mutans attachment to the receptors of the salivary glands. Adsorption of these surface proteins on the teeth matrix surface, where monoclonal antibodies produced against (SA) I/II, which may inhibit adsorption to the teeth\(^{32}\). The connection between host cell and bacteria inhibition by 65–85 percent using designed peptide. This method is very effective in the prevention of caries and other streptococcal infections\(^{33}\). MAM7 is another target of peptide-based anti-adhesive development. MAM7-coupled polymers were used to minimize surface attachment and pathogen infection, like Vibrio parahaemolyticus, Vibrio cholerae, (EPEC), and Yersinia pseudotuberculosis\(^{34}\). Fzeon is an HIV fusion inhibitor peptide that inhibits the viral particles merging to the host cells\(^{35}\). Studies revealed that this approach can be successful anti-adherence therapy when applied to a particular infectious agents.

### 4.3. Dietary anti-adhesion

Several food components were separated and revealed to have a beneficial impact toward several bacterial infection\(^{1}\). Cranberry juice serves to protect toward bacterial infections such as UTIs. Polyphenols and Pro-anthocyanidins have been shown to be biologically active compounds in cranberries\(^{38}\). Pro-anthocyanidins prevent co-aggregation and adhesion of H. pylori, UPEC, and Porphyromonas gingivalis\(^{39}\). Polyphenols and pro-anthocyanidins could attach with flagella or pili, thereby inhibiting attachment of bacterial surface, swarming movement and aggregation onto biofilms. Many Other products, like wine, tea, coffee and plantains, contain anti-adhesion substances\(^{2}\). Dietary products containing a combination of inhibitors or a single inhibitor with a wide range of action.

### 4.4. Anti-adhesion vaccines and antibodies

Several studies have found antibodies to microbial adhesions that have been utilized as an anti-adhesion mechanism. The host might be immunized directly or indirectly indirectly by microbial adhesions adhesions. Vaccination could be achieved with a DNA encoding vaccines\(^{41}\). DNA vaccines include DNA that encodes for an antigen of a specific protein that, when expressed in the host, is capable of creating protective immunity. Vaccinations stimulate humoral as well as cellular immunity against the microorganism. The bacterial infections Prevention is based on adhesion. Vaccination can be accomplished via several approaches. A study revealed that, FimH-based UPEC vaccines immunization prevented 99 percent of infections incidence in murine cystitis mice.

### 4.5. Receptors & adhesions inhibitors

We have to block bacterial adhesion and inhibit attachment to the host cells in order to stop bacterial colonization and infection. There are many possible targets for the drugs that could inhibit such molecules formation (Figure 1). Pilicides are toxins that block the usher-chaperone pathway in pathogens. The inhibitor attacks PapD pilus capperone, thus decreases 90 percent of adhesion to cell line\(^{40}\). Those pilicides disrupt the formation of curli in UPEC through stopping the polymerization of the chaperone protein of type 1 pili\(^{41}\). Sortase, which is a bacteria Gram-positive enzyme, induces adhesions as well as pili formation, thereby, sortase is indeed the target for many inhibitory drugs\(^{42}\).
4.6. **Antibiotics Sub-lethal concentrations**

Studies indicate that minimal antibiotic concentrations below the amount that needed for killing bacteria or microorganism may affect adhesions biochemical and the bacterial surface properties and antibiotics sub minimal inhibitory concentration that minimize attachment to multiple surfaces. Ciprofloxacin Sub-MIC levels against UPEC strains causes a decrease in the bacterial surface hydrophobic nature. Antibiotics in fact increase the adhesion level of some bacteria to catheters such as UPEC. Oxacillin Sub-MIC level for *S. aureus* treatment has significantly increased adherence. On the other hand, sub-MIC reduces adherence. Treatment rifampin decreased the binding of fibronectin of *S. aureus* and diminished the bacteria adhesion to the host surface. Rapid development of antibiotic resistance would be another issue with the sub-MIC use of antibiotics, where antibiotic resistance is more frequently to occur under sub-MIC conditions.

4.7. **Dietary supplements adhesion inhibitors**

Many supplements that inhibits bacterial adherence molecules can be located in many natural foods. Such dietary supplements may be used as anti-adhesion factors. There is no well-known mechanism of action, but there might be analog of receptors and inhibitor of adhesions. The most explored dietary supplement is cranberry, particularly in terms of dental decay and UTIs. Cranberry polyphenols have been shown to reduce a number of bacteria attachment such as *E. coli*. Women who may have ingested cranberry juice throughout a long period of time have shown reduced incidence of bacteriuria. Milk includes antibodies,
glycoproteins, and oligosaccharides that may decrease bacterial attachment. Several pathogens are well known to attach to such a compounds which inhibit their potential to colonize and attach to host cells\(^49\). Human milk is rich in oligosaccharides, which inhibit the attachment of the pathogenic bacteria as well as common enteric pathogen Salmonella fyeris, E. Coli, and V. cholera to cell lines of epithelial\(^{50}\). Bovine Muc1 that extracted from milk of cows effectively inhibit microbial infection. However, there efficient in preventing Gram-positive microbes as S. aureus and Bacillus subtilis is not well, but, it prevents the Gram-negative organisms binding such as Salmonella Typhimurium and E. Coli\(^{51}\).

4.8. Probiotics as an anti-adhesive factors

Probiotic is a beneficial bacteria that block microbes from achieving the essential density needed to cause infection. They may act to decrease the attachment of pathogenic microbes. Probiotic bacteria could eliminate harmful bacteria as well as compete with it for vital growth nutrients\(^{52}\). Probiotics were specifically meant to mimic sugars on target receptors in order to block host cell attachment of toxins produced by pathogenic bacteria, such as E. coli(STEC), ETEC, V. cholera, and shigella toxin-producing\(^{53}\). However, the mechanism of probiotic action is difficult to understand. Probiotics can prevent pathogen adherence by affecting other pathogenesis components and by activating the innate immunity\(^{54}\).

4.9. Glycoconjugates and glycomimetics

The most important factor of microbes ability to induce infection is the adhesion factors attaching to the host cell. Bacterial adhesion molecules found on the microbial surface or on its fimbriae and pili interfere with particular glycans in the host cells. This attachment Inhibition considered an anti-adhesion target for therapies in many infections. The use of appropriate materials that are resistant to environmental state is of great importance. Natural substances for instance can reduce resistance to the destruction by enzymes. Suitable substances should, therefore, be utilize to resolve such a problem. The glycomimetics used as a substitute for traditional sugars that result in higher metabolic selectivity and stability toward the protein goal of desire(4). Efficient anti-adhesion treatment needs a high-affinity monovalent lectin and multivalent compounds containing multiple versions of ligand receptors of mild affinity to a polyvalent scaffold (nanoparticle, polymer, and dendrimer)\(^{55}\).

| Material group | Animal | mechanism | Location | Year | Ref. |
|----------------|--------|-----------|----------|------|------|
| Multivalent adhesion molecule (MAM) 7 coupled polystyrene | In vivo rat model | Blocking assembly or function of pilus | UK | 2017 | (56) |
| PilQ/PilA (QA) antigen of P. aeruginosa (vaccine) | In vivo mouse model | Anti-pili in P. aeruginosa | Iran | 2017 | (57) |
| Compound/Sample | Study Type | Organism/Property | Location | Year | Page |
|-----------------|------------|-------------------|----------|------|------|
| Chitosans (AUM-CS) interacts with negatively charged compounds | In vitro | *K. pneumoniae* and *E. coli* | Italy | 2017 | 58 |
| Salvinolic acid B (SAB) | In vitro | Anti-pilli of *Neisseria meningitidis* | Finland | 2016 | 59 |
| Quercetin | In vitro | *B. subtilis* (prevent bacteria-surface electrostatic attachment through preparing repulsive surfaces) | Egypt | 2016 | 60 |
| *Phaleria macrocarpa* | In vitro | *S. mutans* | Malaysia | 2015 | 61 |
| Essential oils (EOs) | In vitro | *Salmonella* | Tunisia | 2015 | 62 |
| Monoclonal 11B9/61 antibody | In vitro | Pneumococcal type I pilus (RrgA) | America | 2015 | 63 |
| Peptide P2 Peptide P3 | In vitro | AAF-II adhesion of EAEC | India | 2015 | 64 |
| Calixarene-based glycoclusters | In vitro In vivo mouse model | Anti-pilli of *P. aeruginosa* | France | 2014 | 65 |
| Cranberry bioactives | Ex vivo | P-fimbriaL of *E. coli* | New Jersey (United States) | 2013 | 66 |
| Synthetic-mannosides | In vitro | FimH of *E.coli* | Germany | 2013 | 67 |
| Flavonoid rich extract of *Glycyrrhiza glabra* (GutGard) | In vitro | *H. pylori* (inhibit DNA gyrase, dihydrofolate reductase, Protein synthesis) | India | 2012 | 68 |
| *S*-carboxymethylcysteine (*S*-CMC) | In vitro | Platelet-activating factor receptor (PAFR) of *S. pneumoniae* | Japan | 2011 | 69 |
| Melanoidin and non-melanoidin components in coffee | In vitro | *S. mutans* | Italy | 2010 | 70 |
| Cranberry | In vitro | P-fimbria of *E. coli* | France | 2010 | 71 |
Probiotic Lactobacillus rhamnosus GG and Lactobacillus gasseri

Wine components
S. mutans
Italy
2009 (73)

Sialyloligosaccharides (SOS)
V. choleraetoxin (Ctx)
United Kingdom
2009 (74)

Monosaccharide
PA-IL and PA-IIL of P. aeruginosa
France
2008 (75)

Ceramic-composite
S. mutans NCTC 10
Germany
2007 (76)

5. Anti-adhesion therapy advantages and disadvantages

Microorganisms adhesion is a key step in infection and is mainly mediated via protein-carbohydrate interactions. Preventing these interactions appears to be a promising target of anti-adhesion treatment in a variety of infectious diseases. Polyvalent glycoconjugates provide many of the effective anti-adhesive materials, whereas interactions of monovalent protein-sugar are not strong\(^{(77)}\). Anti-adhesion treatment does not elevate microbial resistance because it only prevents microbial attachment to the surface but do not influence microbial activity. This method inhibits biofilm formation and invasion but does not destroy the invasive pathogen, so selective pressure and resistance do not develop for anti-adhesion\(^{(4)}\). It is evident that the existence of several microbial adhesion molecules, as well as the lack of adequate strategies for administering inhibitors to all adhesion molecules, are a huge obstacle to anti-adhesion strategy. Other issues seem to be the weak affinity of unoccupied receptors to microbial ligands as well as the adhesion of popular epitopes to the proteins of human.

Mutations can occur and may influence the effectiveness of anti-adhesion substances. These would even impact the ability of the microorganism to bind directly to the host cell receptor. Point mutations in microbial adhesion molecules may affect tissues in the human body. This problem consideration tells us of the nature of strain-specific as well as anti-adhesive substances that are species-specific to prevent side effects arising from macrobiotics changes.

Environmental resistance conditions is another advantage of this approach. In fact, anti-adhesion agents do not have negative health effects on the host cell but they aren't bactericidal ether\(^{(78)}\).

Conclusions

Antibiotic misuse has led to-resistant strains development, and most of the treatable disease is now a problem. Anti-adhesion treatment includes efforts to block adherence, virulence, and biofilm formation. Those have advantages over conventional antibiotics through suppressing pathogenicity without destroying bacteria. Microbes and bacteria use a wide variety of adherence molecules throughout the adhesion process, thus, numerous molecular interactions might had been blocked to optimize the elimination of the infectious agent from the body. In some cases, failures have occurred in spite of the possible benefits of anti-adhesion therapy. This could be the reason for the absence of wide use of such a particular successful therapy. On the other side, it will be far better
to concentrate on simple tissues rather than on complex tissues when developing anti-adhesions. Clear understanding of such adhesions stereochemistry as well as their membrane-ligand interactions will enable for a practical design of anti-adhesive molecules. Block several targets through wide specificity inhibitors are indeed a great solution. They demonstrate to be of a great efficient with the current antibiotics.

References
1. Krachler AM, Orth K. Targeting the bacteria–host interface: strategies in anti-adhesion therapy. Virulence. 2013;4:284–94.
2. Signoretto C, Canepari P, Stauder M, Vezzulli L, Pruzzo C. Functional foods and strategies contrasting bacterial adhesion. Curr Opin Biotechnol. 2012;23:160–7.
3. Ofek I, Hasty DL, Sharon N. Anti-adhesion therapy of bacterial diseases: prospects and problems. FEMS Immunol Med Microbiol. 2003;38:181–91.
4. Sharon N. Carbohydrates as future anti-adhesion drugs for infectious diseases. Biochim Biophys Acta (BBA) Gen Subj. 2006;1760:527–37.
5. Bibel DJ, Aly R, Shinefield HR. Inhibition of microbial adherence by sphinganine. Can J Microbiol. 1992;38:983–57.
6. Sherman P, Boedeker E. Pilus-mediated interactions of the Escherichia coli strain RDEC-1 with mucosal glycoproteins in the small intestine of rabbits. Gastroenterology. 1987;93:734–43
7. Pak J, Pu Y, Zhang Z-T, Hasty DL, Wu X-R. Tamm–Horsfall protein binds to type 1 fimbriated Escherichia coli and prevents E. coli from binding to uroplakin Ia and Ib receptors. J Biol Chem. 2001;276:9924–30
8. Piotrowski J, Slomiany A, Murty V, Fekete Z, Slomiany B. Inhibition of Helicobacter pylori colonization by sulfated gastric mucin. Biochem Int. 1991;24:749–56
9. Mulvey MA. Adhesion and entry of uropathogenic Escherichia coli. Cell Microbiol. 2002;4:257–71
10. Cozens D, Read RC. Anti-adhesion methods as novel therapeutics for bacterial infections. Expert Rev Anti Infect Ther. 2012;10:1457–68
11. Quintero-Villegas MI, Aam BB, Rupnow J, Sørlie M, Eijsink VG, Hutkins RW. Adherence inhibition of enteropathogenic Escherichia coli by chitoooligosaccharides with specific degrees of acetylation and polymerization. J Agric Food Chem. 2013;61:2748–54
12. Ofek I, Doyle RJ. Common themes in bacterial adhesion. Bacterial adhesion to cells and tissues. Springer, Berlin 1994, pp. 513–61
13. Miörner H, Johansson G, Kronvall G. Lipoteichoic acid is the major cell wall component responsible for surface hydrophobicity of group A streptococci. Infect Immun. 1983;39:336–43
14. Sharon N. Bacterial lectins, cell-cell recognition and infectious disease. FEBS Lett. 1987;217:145–57
15. Cundell DR, Gerard NP, Craig G, Idanpaan-Heikkila I, Tuomanen EL. Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet-activating factor. Nature. 1995;377:435
16. Chen SL, Hung C-S, Xu J, Reigstad CS, Magrini V, Sabo A, et al. Identification of genes subject to positive selection in uropathogenic strains of Escherichia coli: a comparative genomics approach. Proc Natl Acad Sci. 2006;103:5977–82.
17. Svensson A, Larsson A, Emtenäss H, Hedenström M, Fex T, Hultgren SJ, et al. Design and evaluation of pilicides: potential novel antibacterial agents
directed against uropathogenic *Escherichia coli*. Chembiochem. 2001;2:915–8
18. Pinkner JS, Bengtsson C, Edvinsson S, Cusumano CK, Rosenbaum E, Johansson LB, et al. Design and synthesis of fluorescent pilicides and curlicides: bioactive tools to study bacterial virulence mechanisms. Chem A Eur J. 2012;18:4522–32.
19. Hartlova A, Cerveny L, Hubalek M, Krocova Z, Stulik J. Membrane rafts: a potential gateway for bacterial entry into host cells. Microbiol Immunol. 2010;54:237–45
20. Svensson M, Frendeus B, Butters T, Platt F, Dwre R, Svanborg C. Glycolipid depletion in antimicrobial therapy. Mol Microbiol. 2003;47:453–61.
21. Margalit M, Ash N, Zimran A, Halkin H. Enzyme replacement therapy in the management of longstanding skeletal and soft tissue salmonella infection in a patient with Gaucher’s disease. Postgrad Med J. 2002;78:564–5.
22. Bernbom N, Jörgensen RL, Ng Y, Meyer R, Kingshott P, Vejborg RM, et al. Bacterial adhesion to stainless steel is reduced by aqueous fish extract coatings. Biofilms. 2006;3:25–36
23. Chen L, Wen Y-m. The role of bacterial biofilm in persistent infections and control strategies. Int J Oral Sci. 2011;3:66
24. Svensson M, Platt FM, Svanborg C. Glycolipid receptor depletion as an approach to specific antimicrobial therapy. FEMS Microbiol Lett. 2006;258:1–8
25. Okuda K, Hanada N, Usui Y, Takeuchi H, Koba H, Nakao R, et al. Inhibition of *Streptococcus mutans* adherence and biofilm formation using analogues of the SspB peptide. Arch Oral Biol. 2010;55:754–62
26. Moon HW, Bunn TO. Vaccines for preventing enterotoxigenic *Escherichia coli* infections in farm animals. Vaccine. 1993;11:213–20
27. Sharon N, Ofek I. Safe as mother’s milk: carbohydrates as future anti-adhesion drugs for bacterial diseases. Glycoconjug J. 2000;17:659–64
28. Bouckaert J, Berglund J, Schembri M, De Genst E, Cools L, Wuhrer M, et al. Receptor binding studies disclose a novel class of high-affinity inhibitors of the *Escherichia coli* FimH adhesin. Mol Microbiol. 2005;55:441–55
29. Jiang X, Abgottspon D, Kleeb S, Rabbani S, Scharenberg M, Wittwer M, et al. Antiadhesion therapy for urinary tract infections. A balanced PK/PD profile proved to be key for success. J Med Chem. 2012;55:4700–13
30. Almant M, Moreau V, Kovensky J, Bouckaert J, Gouin SG. Clustering of *Escherichia coli* type-1 fimbrial adhesins by using multimeric heptyl α-D-Mannoside probes with a carbohydrate core. Chem A Eur J. 2011;17:10029–38.
31. Chemani C, Imberty A, de Bentzmann S, Pierre M, Wimmerová M, Guery BP, et al. Role of LecA and LecB lectins in *Pseudomonas aeruginosa*-induced lung injury and effect of carbohydrate ligands. Infect Immun. 2009;77:2065–75.
32. Ukkonen P, Varis K, Jernfors M, Herva E, Jokinen J, Ruokokoski E, et al. Treatment of acute otitis media with an antiadhesive oligosaccharide: a randomised, double-blind, placebo-controlled trial. Lancet. 2000;356:1398–402.
33. Lillehoj EP, Kim BT, Kim KC. Identification of *Pseudomonas aeruginosa* flagellin as an adhesin for Muc1 mucin. Am J Physiol Lung Cell Mol Physiol. 2002;282:L751-L6
34. Ma J, Hunjan M, Smith R, Lehner T. Specificity of monoclonal antibodies in local passive immunization against Streptococcus mutans. Clin Exp Immunol. 1989;77:331
35. Munro GH, Evans P, Todryk S, Buckett P, Kelly CG, Lehner T. A protein fragment of streptococcal cell surface antigen I/II which prevents adhesion of Streptococcus mutans. Infect Immun. 1993;61:4590–8
36. Krachler AM, Mende K, Murray C, Orth K. In vitro characterization of multivalent adhesion molecule 7-based inhibition of multidrug-resistant bacteria isolated from wounded military personnel. Virulence. 2012;3:389–99
37. Lalezari JP, Henry K, O’hearn M, Montaner JS, Piliero PJ, Trotter B, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med. 2003;348:2175–85.
38. Labrecque J, Bodet C, Chandad F, Grenier D. Effects of a high-molecular-weight cranberry fraction on growth, biofilm formation and adherence of Porphyromonas gingivalis. J Antimicrob Chemother. 2006;58:439–43.
39. Burger O, Weiss E, Sharon N, Tabak M, Neeman I, Ofek I. Inhibition of Helicobacter pylori adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice. Crit Rev Food Sci Nutr. 2002;42:279–84.
40. Pinkner JS, Remaut H, Buelens F, Miller E, Åberg V, Pemberton N, et al. Rationally designed small compounds inhibit pilus biogenesis in uropathogenic bacteria. Proc Natl Acad Sci. 2006;103:17897–902.
41. Eidam O, Dworkowski FS, Glockshuber R, Grüter MG, Capitani G. Crystal structure of the ternary FimC–FimFt–FimDN complex indicates conserved pilus chaperone–subunit complex recognition by the usher FimD. FEBS Lett. 2008;582:651–5.
42. Ton-That H, Schneewind O. Anchor structure of staphylococcal surface proteins IV. Inhibitors of the cell wall sorting reaction. J Biol Chem. 1999;274:24316–20.
43. Mortensen NP, Fowlkes JD, Maggart M, Doktycz MJ, Nataro JP, Drusano G, et al. Effects of sub-minimum inhibitory concentrations of ciprofloxacin on enteroaggregative Escherichia coli and the role of the surface protein dispersin. Int J Antimicrob Agents. 2011;38:27–34
44. Wojnicz D, Jankowski S. Effects of subinhibitory concentrations of amikacin and ciprofloxacin on the hydrophobicity and adherence to epithelial cells of uropathogenic Escherichia coli strains. Int J Antimicrob Agents. 2007;29:700–4
45. Rasigade JP, Moulay A, Lhoste Y, Tristan A, Bes M, Vanden Bosch F, et al. Impact of sub-inhibitory antibiotics on fibronectin-mediated host cell adhesion and invasion by Staphylococcus aureus. BMC Microbiol. 2011;11:263
46. 72.Cars O. Pharmacokinetics of antibiotics in tissues and tissue fluids: a review. Scand J Infect Dis. 1991;74:23–33.
47. Liu Y, Pinzón-Arango PA, Gallardo-Moreno AM, Camesano TA. Direct adhesion force measurements between E. coli and human uroepithelial cells in cranberry juice cocktail. Mol Nutr Food Res. 2010;54:1744–52
48. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. BMJ. 2001;322:1571
49. Morrow AL, Ruiz-Palacios GM, Jiang X, Newburg DS. Human-milk glycans that inhibit pathogen binding protect breast-feeding infants against infectious diarrhea. J Nutr. 2005;135:1304–7

50. Coppa GV, Zampini L, Galeazzi T, Facinelli B, Ferrante L, Capretti R, et al. Human milk oligosaccharides inhibit the adhesion to Caco-2 cells of diarrheal pathogens: Escherichia coli, Vibrio cholerae, and Salmonella fyris. Pediatr Res. 2006;59:377–82

51. Parker P, Sando L, Pearson R, Kongsuwan K, Tellam RL, Smith S. Bovine Muc1 inhibits binding of enteric bacteria to Caco-2 cells. Glycoconj J. 2010;27:89–97

52. Candela M, Perna F, Carnevali P, Vitali B, Ciati R, Gionchetti P, et al. Interaction of probiotic Lactobacillus and Bifidobacterium strains with human intestinal epithelial cells: adhesion properties, competition against enteropathogens and modulation of IL-8 production. Int J Food Microbiol. 2008;125:286–92.

53. Focareta A, Paton JC, Morona R, Cook J, Paton AW. A recombinant probiotic for treatment and prevention of cholera. Gastroenterology. 2006;130:1688–95.

54. Moshiri M, Dallal MMS, Rezaei F, Douraghi M, Sharifi L, Noroozbabaei Z, et al. The effect of lactobacillus acidophilus PTCC 1643 on cultured intestinal epithelial cells infected with Salmonella enterica serovar Enteritidis. Osong Public Health Res Perspect. 2017;8:54.

55. Cecioni S, Imberty A, Vidal S. Glycomimetics versus multivalent glycoconjugates for the design of high affinity lectin ligands. Chem Rev. 2014;115:525–61.

56. Roberts PA, Huebinger RM, Keen E, Krachler A-M, Jabbari S. Predictive modelling of a novel anti-adhesion therapy to combat bacterial colonisation of burn wounds. arXiv preprint arXiv:170807062. 2017.

57. Gholami M, Chirani AS, Razavi S, Falak R, Irjani G. Immunogenicity of a fusion protein containing PilQ and disulfide turn region of PilA from Pseudomonas aeruginosa in mice. Lett Appl Microbiol. 2017;65:439–445.

58. Campana R, Casettari L, Ciandrini E, Illum L, Baffone W. Chitosans inhibit the growth and the adhesion of Klebsiella pneumoniae and coli clinical isolates on urinary catheters. Int J Antimicrob Agents. 2017;50:135–41.

59. Huttunen S, Toivanen M, Liu C, Tikkanen-Kaukanen C. Novel anti-infective potential of salvianolic acid B against human serious pathogen Neisseria meningitidis. BMC Res Notes. 2016;9:25.

60. Raie DS, Mhatre E, Thiele M, Labena A, El-Ghannam G, Farahat LA, et al. Application of quercetin and its bio-inspired nanoparticles as anti-adhesive agents against Bacillus subtilis attachment to surface. Mater Sci Eng C. 2017;70:753–62.

61. Heana NY, Othmanb SNAM, Basarb N, Jemona K. Antibiofilm and antiadhesion activities of Phaleria macrocarpa against oral Streptococcus mutans. J Teknol. 2015;77:31–35

62. Miladi H, Mili D, Slama RB, Zouari S, Ammar E, Bakhrouf A. Antibiofilm formation and anti-adhesive property of three mediterranean essential oils against a foodborne pathogen Salmonella strain. Microbial Pathog. 2016;93:22–31.

63. Amerighi F, Valeri M, Donnarumma D, Maccari S, Moschioni M, Taddei A, et al. Identification of a monoclonal antibody against pneumococcal pilus 1 ancillary protein impairing bacterial
adhesion to human epithelial cells. J Infect Dis. 2015;213:516–22.
64. Gupta D, Sarkar S, Sharma M, Thapa B, Chakraborti A. Inhibition of enteroaggregative Escherichia coli cell adhesion in-vitro by designed peptides. Microbial Pathog. 2016;98:23–31
65. Boukerb AM, Rousset A, Galanos N, Mear J-B, Thepaut M, Grandjean T, et al. Antiadhesive properties of glyoclusters against Pseudomonas aeruginosa lung infection. J Med Chem. 2014;57:10275–89
66. Kaspar KL, Howell AB, Khoo C. Ex vivo anti-adhesion activity of a proanthocyanidin standardized cranberry powder beverage. FASEB J. 2013;27:1079.42–42
67. Fessele C, Lindhorst TK. Effect of aminophenyl and aminothiahexyl α-d-glycosides of the manno-, gluco-, and galacto-series on type I fimbriae-mediated adhesion of Escherichia coli. Biology. 2013;2:1135–49.
68. Asha MK, Debraj D, Edwin JR, Srikanth H, Muruganantham N, Dethe SM, et al. In vitro anti-Helicobacter pylori activity of a flavonoid rich extract of Glycyrrhiza glabra and its probable mechanisms of action. J Ethnopharmacol. 2013;145:581–6.
69. Sumitomo T, Nakata M, Yamaguchi M, Terao Y, Kawabata S. S-carboxymethylcysteine inhibits adherence of Streptococcus pneumoniae to human alveolar epithelial cells. J Med Microbiol. 2012;61:101–8
70. Stauder M, Papetti A, Mascherpa D, Schito AM, Gazzani G, Pruzzo C, et al. Antiadhesion and antibiofilm activities of high molecular weight coffee components against Streptococcus mutans. J Agric Food Chem. 2010;58:11662–6
71. Howell AB, Botto H, Combescure C, Blanc-Potard A-B, Gausa L, Matsumoto T, et al. Dosage effect on uropathogenic Escherichia coli anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: a multicentric randomized double blind study. BMC Infect Dis. 2010;10:94
72. Burkholder KM, Bhunia AK. Salmonella enterica serovar Typhimurium adhesion and cytotoxicity during epithelial cell stress is reduced by Lactobacillus rhamnosus GG. Gut Pathog. 2009;1:14
73. Daglia M, Stauder M, Papetti A, Signoretto C, Giusto G, Canepari P, et al. Isolation of red wine components with anti-adhesion and anti-biofilm activity against Streptococcus mutans. Food Chem. 2010;119:1182–8.
74. Sinclair HR, Kemp F, de Slegte J, Gibson GR, Rastall RA. Carbohydrate-based anti-adhesive inhibition of Vibrio cholerae toxin binding to GM1-OS immobilized into artificial planar lipid membranes. Carbohydr Res. 2009;344:1968–74.
75. McEwan NA, Rème CA, Gatto H, Nuttall TJ. Monosaccharide inhibition of adherence by Pseudomonas aeruginosa to canine corneocytes. Vet Dermatol. 2008;19:221–5
76. Rosentritt M, Hahnel S, Gröger G, Mühlfriedel B, Bürgers R, Handel G. Adhesion of Streptococcus mutans to various dental materials in a laminar flow chamber system. J Biomed Mater Res Part B Appl Biomater. 2008;86:36–44.
77. Sattin S, Bernardi A. Glycoconjugates and glycomimetics as microbial anti-adhesives. Trends Biotechnol. 2016;34:483–95.
78. http://www.cdc.gov/drugresistance/pdf/hai-patient-empowerment_dpk.pdf